Functioning and Health of Children and Adolescents with Heritable Connective Tissue Disorders and their Parents





Jessica Warnink-Kavelaars

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CHAPTER 1

"Me and my friends at the gym" by Amarins (8 years)

General introduction

Heritable Connective Tissue Disorders

Heritable Connective Tissue Disorders (HCTD) are characterized by pathological connective tissue fragility and multisystemic involvement. [1-6] The phenotypes of the most common HCTD, Marfan syndrome (MFS),[2, 3] Loeys-Dietz syndrome (LDS) [4, 5, 7] and Ehlers-Danlos syndromes (EDS),[6] show similarities in cardiovascular (aortic aneurysm, mitral valve prolapse), musculoskeletal (scoliosis, hindfoot deformity, pes planus, anterior chest deformity, joint hypermobility), and cutaneous features (striae, skin hyperextensibility, tissue fragility) that can evolve in childhood. [1] The impact of HCTD on functioning and health of children and adolescents may also show overlap between the different disorders. To intervene the consequences of HCTD in childhood it is critical to understand the impact of HCTD on functioning and health including Health-Related Quality of Life (HRQoL) and mental health of children and adolescents. Furthermore it is important to explore and understand the interactions between domains and the facilitating and limiting factors. Thereafter, tailored interventions should be developed to improve functioning and health of children and adolescents and to prevent reoccurrence of problems.

A diagnosis of HCTD is based on clinical criteria and molecular confirmation. Some children and adolescents may not fit the clinical criteria yet because of the age dependent nature of some HCTD clinical manifestations and the variable presentation. Therefore, children and adolescents with HCTD or suspicion of HCTD need special consideration and follow-up. [8]

The diagnosis MFS relies on a set of defined clinical cardiovascular, ocular, musculoskeletal, facial and cutaneous manifestations established from the revised Ghent nosology. [3] MFS is an autosomal dominant HCTD, occurs de novo in a quarter of patients and is caused by heterozygous mutations in *FBN1* encoding for the extracellular matrix protein fibrillin-1. [9] The prevalence is approximately 6.5 per 100.000 individuals. [10] The cardinal clinical manifestations are aortic root aneurysm and ectopia lentis. Most selective systemic MFS features are included in the "systemic score". Points (max 20) are received for the features presence and severity (wrist and/or thumb sign, anterior chest wall deformity, hindfoot deformity, pes planus, pneumothorax, dural ectasia, protrusio acetabuli, reduced upper/lower segment and increased arm span/height ratio, scoliosis, thoracolumbar kyphosis, reduced elbow extension, three of five facial features, skin straie, severe myopia, mitral valve prolapse). [8, 11-15] A score ≥ 7 indicates systemic involvement in adults; in children this score can be lower because of the evolving systemic features. In the absence of any family history, the presence of aortic root dilatation z-score ≥ 3 (below 20 years of age) and ectopia lentis or *FBN1* or a systemic score ≥ 7 are sufficient to diagnose a patient with MFS. In the presence of a family history, the presence of ectopia lentis or aortic root dilatation z-score ≥ 3 (below 20 years of age) or a systemic score ≥ 7 is sufficient for a diagnosis of MFS. [3]

The diagnosis LDS is based on a molecular confirmation of a causative mutation because no formal diagnostic clinical criteria have been established yet. [4, 5, 7, 16, 17] LDS is an autosomal dominant HCTD and occurs de novo in two third of patients. It is caused by *TGFB2/3, TGFBR1/2, SMAD2/3,* mutations encoding for components of the transforming beta (TGFβ) signaling pathway, including the cytokines (*TGFB2/3*), the receptors (*TGFBR1/2*), and the downstream effectors (*SMAD2/3*). [4] The prevalence is unknown. Genetic testing should be considered in case of recognition of LDS features within the cardiovascular, craniofacial, skeletal and cutaneous systems. Cardiovascular features comprise aortic root aneurysm, arterial tortuosity, early arterial dissections (onset on an earlier age than in patients with MFS), bicuspid aortic valve and mitral valve insufficiency. Craniofacial features involve cleft plate, bifid uvula, hypertelorism and craniosynostosis. Musculoskeletal features include pectus deformities, scoliosis, joint laxity, pes equinovarus and/or pes planus, cervical spine malformation and/or instability, spondylolisthesis, acetabular protrusion and joint hypermobility including dislocations of the hip and recurrent subluxations, although some patients show contractures. Tall stature and arachnodactyly, typical MFS features, are present in some. LDS can be distinguished from MFS by the triad of hypertelorism, bifid uvula or cleft palate, widespread aortic and arterial aneurysm and tortuosity which tend to be more severe. [1] LDS cutaneous features involve easy bruising and velvety, thin, translucent skin and show significant similarities with EDS.

The diagnosis EDS is based on symptoms of joint hypermobility, skin hyperextensibility, tissue fragility and a molecular confirmation, except for hypermobile EDS (hEDS). In hEDS, a genetic cause has not yet been determined and the diagnosis relies on clinical criteria only. EDS is a clinically heterogeneous group. The 2017 international classification of the Ehlers-Danlos syndromes [6] recognizes 13 subtypes: Classical EDS, Classical-like EDS, Cardiac-valvular EDS, Vascular EDS, hEDS, Arthrochalasia EDS, Dermatosparaxis EDS, Kyphoscoliotic EDS, Brittle Cornea syndrome, Spondylodysplastic EDS, Musculocontractural EDS, Myopathic EDS and Periodontal EDS. The EDS inheritance pattern is, depending on the subtype, either autosomal dominant or autosomal recessive and caused by variants in several genes (*COL5A1, COL5A2, COL1A1, TNXB, COL1A2, COL3A1, COL1A1, ADAMTS2, PLOD1, FKBP14, ZNF469, PRDM5, B4GALT7, B3GALT6, SLC39A13, CHST14, DSE, COL12A1, C1R, C1S*). Each EDS subtype shows a different prevalence from 1 in 5.000 (hEDS) to < 1 in 1000.000 (Cardiac-valvular EDS). To distinguish between subtypes, sets of specific clinical criteria are developed, comprising major and minor clinical criteria. [6]

Functioning and health of children and adolescents with chronic diseases

Globally, over the past three decades, the prevalence of chronic diseases and aggregated disability in children and adolescents has increased. [18-20] Improved education, diagnostics and new treatments have resulted in better medical care and higher survival rates for congenital and acquired childhood disorders. [18] As a result, the percentage of children with chronic diseases during childhood and adolescence has increased.

In the Netherlands, approximately 1.300.000 children and young adults, [21] aged 0-25, of which approximately 500.000 children and adolescents [22] aged 0 to 18 years, are living with a chronic disease. Internationally, several definitions of chronic disease and chronic health conditions are used. [23] Dutch consensus was attained on a definition of pediatric chronic disease consisting of four criteria: "(1) it occurs in children aged 0 to 18 years; (2) the diagnosis is based on medical scientific knowledge and can be established using reproducible and valid methods or instruments according to professional standards; (3) it is not (yet) curable or, for mental health conditions, if it is highly resistant to treatment and (4) it has been present for longer than three months or it will, very probably, last longer than three months, or it has occurred three times or more during the past year and will probably reoccur." [24]

Pediatric chronic diseases can impact functioning and health. Children and adolescents with chronic heart diseases [25] and Juvenile Idiopathic Arthritis [26-28] were reported to have limited physical activities, [25, 26] school attendance, extracurricular activities, [25] play and leisure, [27] and school participation. [28] Compared to healthy children, children with chronic diseases reported significantly lower HRQoL. [29-31] Reviews on children and adolescents with chronic diseases and within disease clusters also reported difficulties regarding daily functioning and quality of life. [29, 32-34] Furthermore, pediatric chronic diseases have been found to evoke behavioral and emotional problems. [35, 36]

Functioning and health of children and adolescents with Heritable Connective Tissue Disorders

There are few descriptive and quantitative studies on the impact of pediatric HCTD on functioning and health. Descriptive studies in children and adolescents with MFS and hEDS, reported fatigue and pain to negatively impact (physical) functioning [12, 37-41] with a high incidence of pain-related disability [39, 41] and deteriorating physical functioning over time. [42] Quantitative studies in children and adolescents with hEDS and Hypermobility Spectrum Disorder [43] (HSD, the current label for patients with joint hypermobility with musculoskeletal complications, who do not fulfil the criteria for hEDS), reported increased pain and fatigue, [40] generalized hyperalgesia, [44] and improvement of disability after following an outpatient multidisciplinary rehabilitation treatment program. [45] Moreover, national and international MFS and cardiovascular guidelines recommend modifications and restrictions in participation of competitive and contact sports that would cause chest or eye trauma or put added stress on the aorta. [12, 13, 16, 46-48]

Regarding adults with HCTD, it has been reported that patients with MFS, LDS, EDS and hEDS perceived a negative impact of the disorder on their functioning and health. They reported increased HCTD-related physical problems, increased pain and fatigue, limited activities and restricted participation in leisure, sports and work. Furthermore they perceived psychosocial problems, a low self-esteem and limited support. [1, 4, 7, 16, 17, 41, 49-72]

Until now, it is largely unknown whether children and adolescents with HCTD suffer from decreased HRQoL. In a review on psychosocial outcomes of children with MFS, [56] self-reported HRQoL was decreased in two studies, [73, 74] and unimpaired in another study. [75] Children with EDS [74] and hEDS/HSD [40, 76] also reported decreased HRQoL. To our knowledge, data on HRQoL in children with LDS are lacking.

Adults with MFS, LDS, and EDS reported their physical condition and cardiovascular problems to negatively influence quality of life. [17, 51, 56] Moreover, adults with hypermobile hEDS/HSD reported decreased physical and psychosocial HRQoL. [41, 58, 66, 67, 77, 78]

Studies on mental health in children and adolescents with HCTD are also limited. An older study reported attention deficit disorder with or without hyperactivity in 17% of children with MFS. [79] A psychiatric disorder (most commonly anxiety and depression) was reported in 41.3% of children with hEDS/HSD. [40] To our knowledge, no studies have been published on mental health in children with LDS and EDS.

A review on adults with MFS reported co-occurrence of psychiatric disorders and MFS, but firm conclusions were not drawn. [80] Adults with EDS, hEDS/HSD reported an increased risk of psychiatric disorders. [68-72, 78, 81-84]

Parenting children and adolescents with Heritable Connective Tissue Disorders

As a result of the increased prevalence of chronic diseases and disability in children and adolescents [18-20] the percentage of parents caring for a child with chronic diseases also

increased. Caring for a child with chronic diseases like HCTD can affect the parents' care responsibilities and increase the parents' distress and everyday problems.

A meta-analysis reported that among parents of children with chronic diseases, most parents exhibited satisfactory parent-child relationships and parenting styles; although some parents had difficulty finding appropriate levels of protective behavior and building a positive parent-child relationship. [85] Furthermore, several studies reported parents of a child with chronic diseases suffering from anxiety, depression [86] and increased stress. [87] Parents, mothers in particular, were described to be disadvantaged in participation in society, because they had to combine caring for their children and family with work and leisure. [88]

Parents of children with congenital heart disorders experienced parental burden due to increased stress, challenges to cope with the diagnosis, dealing with the problems facing their child, fear for cardiovascular complications and lack of social support. [89-91] Furthermore, parents of children with other diseases like cancer, [92] mucopolysaccharidosis type III, [93] inflammatory bowel disease, [94] Down syndrome [95] and chronic diseases of any type, [96] screened by the Distress thermometer for Parents of a chronically ill child (DT-P), [97, 98] reported significantly higher distress and/or more often everyday problems compared to control-group parents. These and other studies also reported significant differences in distress levels of mothers compared to fathers. [86, 92, 93, 95, 99, 100] Parents of children with HCTD may also be confronted with similar problems.

It becomes even more complicated for parents and their children with autosomal dominant heritable disorders. If the parent is affected, then each child has a 50 % chance of inheriting the mutation. Therefore, in many families, both a parent and one or more children are diagnosed with HCTD and require regular medical follow-up [12, 13, 46-48] because of the risk of developing medical complications. [1-6, 11, 14, 50, 101, 102] These parents have extensive caregiving responsibilities, both for their children with HCTD and for themselves or their partner with HCTD. This may contribute to distress and everyday problems. Studies on distress in parents of children with HCTD who themselves suffer from the same condition; as well as studies on distress in healthy parents caring for a child and/or partner with HCTD are, to our knowledge, not available.

In addition, parents reported the adverse effects of parental chronic illness on their HRQoL [88, 103] and a tendency of limited social and family activities for all family members. [104] Furthermore, studies on adults on the negative impact of HCTD on functioning and health provide a better understanding of the distress of parents with HCTD. [1, 4, 7, 16, 17, 41, 49-72]

Clinical care for children and adolescents with Heritable Connective Tissue Disorders in the Netherlands and Europe.

In the Netherlands, clinical care for children and adolescents with HCTD, is organized within the expert centers Marfan syndrome and related (connective tissue) disorders, including the University Medical Centers of Amsterdam, Groningen, Leiden, Maastricht, Nijmegen and Rotterdam. The expert centers comprise a multidisciplinary team, which is advised by the Dutch MFS guideline. [13] The "Dutch Network Marfan and related disorders" represents all expert centers, professionals who work with patients with HCTD, researchers and patient associations. The network goals are to improve the quality of care for children, adolescents and adults with HCTD, to share knowledge, to collaborate in research projects, to develop educational courses and to maintain the Dutch guideline MFS. In Europe, the expert centers are affiliated with the European Reference Networks (ERN) Skin, an ERN on rare and complex skin conditions (thematic group Mendelian Connective Tissue Disorders); VASCERN, an ERN on rare multisystemic vascular diseases, and Reconnet, an ERN on rare and complex connective tissue and musculoskeletal diseases. The ERN is a network comprised of healthcare professionals throughout Europe and its goals are to address complex or rare diseases that require highly specialized treatment and a concentration of knowledge and resources.

Models of Functioning and Health and definitions

To understand functioning and health of children and adolescents with HCTD, it is important to map everyday problems and indicate interactions between physical features, activities, participation, environmental and personal factors, HRQoL and mental health.

The World Health Organization (WHO)[105] developed the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) to map functioning, disability and health. In this model "Functioning" is defined as all body functions, activities and participation; "Disability" as impairments, activity limitations and participation restrictions; and "Health" as the complete physical, mental and social functioning. Disability is a derivative of functioning and therefore, in this thesis, we prefer to use the terms "Functioning and Health". In addition, in this thesis we use the definitions of the WHO for HRQoL and mental health which are defined 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. The United Nations Convention on the Rights of the Child [106] defines "children" as those persons below the age of 18 years. The WHO [105] defines "adolescence" as the transitional stage of physical and psychological development that generally occurs during the period from puberty to adulthood. Therefore, in this thesis we choose to refer to "children and adolescents". Furthermore, other overlapping terms used by the WHO are "youth" defined as those persons between 15–24 years.

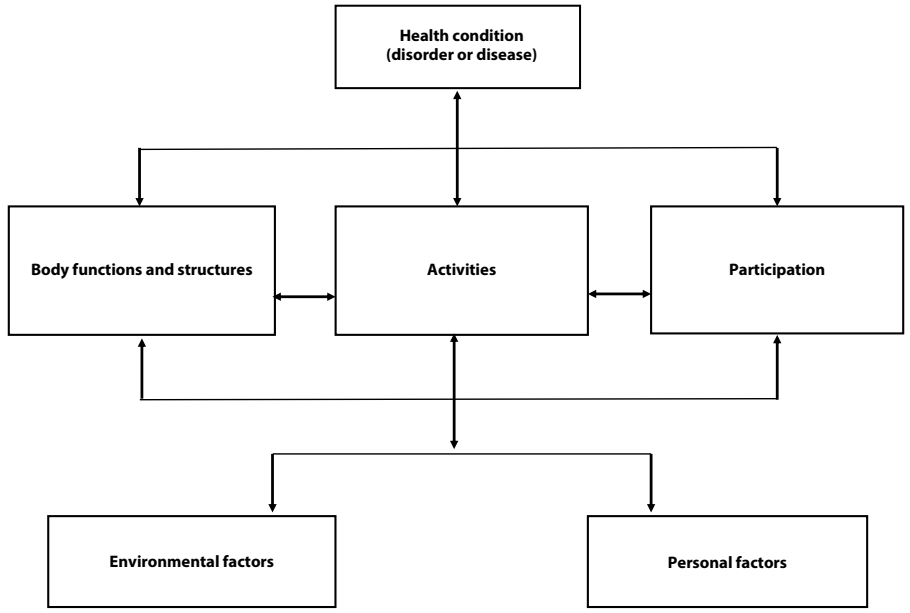

Figure 1. International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) model [105]

The ICF-CY model consists of five interacting domains: "Body functions and structures", "Activities", "Participation", "Environmental factors" and "Personal factors". "Body Functions" are defined as physiological functions of body systems and "Body Structures" as anatomical parts of the body such as organs. Impairments are problems in body function or structure such as a significant deviation or loss. "Activity" is defined as the execution of a task or action by a child or adolescent. Activity limitations are difficulties a child may have in executing activities (mobility-, selfcare-, household tasks e.g.). "Participation" refers to involvement in daily life. Participation restrictions are problems a child or adolescent experience in involvement in daily life situations (friendships, school, work, sport, leisure, playing). "Environmental factors" are defined as the physical, social and attitudinal environment in which children live and conduct their lives (support and relationships, environmental attitudes, services, products and technology). "Personal factors" include the particular background of a child's life, like gender, age, coping strategies, overall behavior pattern, planning, self-esteem, social background, education and other factors that influence functioning. The ICF-CY did not classify this domain yet given the social and cultural variability. Qualifiers are used to record the presence and severity of a problem in one of the ICF-CY domains. Body function and structures, are classified by the presence and degree of an impairment (no impairment, mild, moderate, severe and complete). For the classifications of in the activity and participation domains, two important qualifiers are provided. The performance qualifier describes what a child does in his or her current environment. The capacity qualifier describes the child's ability to execute a task or an action. The ICF-CY provides a common and global language and facilitates documentation of functioning, disability and health of children and adolescents.

Aim and outline of this thesis

This thesis aims to explore and investigate the impact of HCTD on functioning and health, including HRQoL and mental health, of children, adolescents and their parents.

Chapter 1 presents a general introduction to HCTD, the current literature on functioning and health of children with chronic diseases and HCTD as well as distress in parents. In addition, national and international clinical care of children and adolescents with HCTD is outlined. The ICF-CY model is explained and definitions are provided.

Part 1 Functioning and health of children and adolescents with Marfan syndrome, their parents and family

Chapter 2 reports parents' perspectives on the impact of MFS functioning and health of their children with MFS, aged 4 to12 years, and the impact of caring for a child with MFS on parents and family. Semi-structured interviews and focus groups were conducted with parents of children with MFS, aged 4 to12 years. **Chapter 3** reports the adolescents' perspectives on the impact of MFS on functioning and health and their support needs. Semi-structured interviews were conducted with adolescents with MFS, aged 12 to 18 years. **Chapter 4** investigates distress and everyday problems of parents of a child with MFS on the standardized validated questionnaire Distress Thermometer for Parents of a

chronically ill child (DT-P). Parents of a child with MFS were compared to a representative general population sample.

Part 2 Functioning and health of children and adolescents with Heritable Connective Tissue Disorders

Chapters 5 and 6 report the impact of HCTD on pain, fatigue, activities, participation, HRQoL and mental health in children and adolescents with HCTD using standardized validated questionnaires. A large group of children with HCTD were compared to representative general population samples. In addition, subgroups of children and adolescents with MFS, LDS, EDS, and hEDS were compared to representative general population samples.

Chapter 7 presents the overall conclusions of the individual studies in this thesis and discusses key findings in a broader perspective regarding clinical relevance of the findings, methodological considerations, implications for clinical care and directions for future research. A new model is presented to explore, explain and discuss child and adolescent functioning and health including HRQoL and mental health as well as the interactions between domains.

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CHAPTER 2

"Me and my family" by Ariana (5 years)

Marfan syndrome in childhood: Parents' perspectives of the impact on daily functioning of children, parents and family; a qualitative study

Warnink-Kavelaars J, Beelen A, Dekker S, Nollet F, Menke LA, Engelbert RHH. *BMC Pediatr*. 2019;19(1):262. Published 2019 Jul 29. doi:10.1186/s12887-019-1612-6

Abstract

Background Marfan syndrome (MFS) is a Heritable Connective Tissue Disorder caused by a defect in *FBN1*. The diagnosis is based on the revised Ghent criteria. The main features involve the cardiovascular, musculoskeletal, ophthalmic, pulmonary systems and facial features. Although the clinical manifestations of MFS in children are addressed in several studies, literature on the impact of MFS on daily functioning is restricted to pediatric advice on sports and leisure participation. Therefore, the full impact of MFS on daily functioning remains unclear. The aim of this qualitative study was to explore parents' perspectives on the impact of MFS on daily functioning of children with MFS aged 4-12 years, themselves and family regarding functional performance, activities, participation, personal and environmental factors, and disease burden.

Methods In this qualitative study parents participated in individual semi-structured interviews (n=10) and 3 focus groups (n=5, n=5 and n=6). Meetings were transcribed, and data analyzed using thematic analysis. Meaningful concepts were coded, concepts concerning children with MFS were linked to the International Classification of Functioning, Disability and Health for Children and Youth. Thereafter themes were identified and interpreted.

Results Parents reported their children could not keep up with peers because of fatigue, pain and physical impairments. Children experienced participation restrictions in school, sports, play and other leisure activities. Parents reported their child as being different due to physical appearance, which provoked unsupportive attitudes. Parental burden was caused by high care needs, lack of support, limited social life, and concerns about the child's development. Family burden was caused by adjusted and complex family schedules, other family members with MFS, and reproductive planning decision-making, whereas family cohesiveness and caring were positively perceived factors.

Conclusions Parents perceived a large impact of MFS on daily functioning of their children with MFS, themselves and their family. More awareness among medical professionals involved in the care of children with MFS, is needed to address and discuss child, parental and family support needs. Then medical professionals can provide tailored interventions, rehabilitation and/or educational programs to empower and improve daily functioning of children with MFS, parents and family.

Background

Marfan syndrome (MFS) is a Heritable Connective Tissue Disorder (HCTD) caused by a defect in *FBN1*. The diagnosis is based on the revised Ghent criteria. [1] The main features involve the cardiovascular (aortic aneurysm, mitral valve prolapse), musculoskeletal (increased arm span/height and reduced upper/lower segment ratios, arachnodactyly, hypermobility/contractures, scoliosis, hindfoot deformity, pes planus, pectus excavatum and carinatum), ophthalmic (ectopia lentis, severe myopia) and pulmonary (pneumothorax) systems, skin striae and facial features (dolichocephaly, enophthalmos, downward slanting of the eyes, malar hypoplasia and retrognathia). [2-7]

Although the clinical manifestations of MFS in children are thoroughly addressed in several studies, literature on the impact of MFS on daily functioning is restricted to pediatric advice on sports and leisure participation, based on expert opinions and cardiovascular research [3, 5] and a study on pediatric quality of life. [8] Therefore, the full impact of MFS on daily functioning of children, parents and family remains unclear. This lack of knowledge hampers health care professionals and multi-disciplinary teams who are involved in the care of children with MFS and their families from providing evidence-based advice to parents and children asking about the everyday consequences of MFS and available interventions to improve daily functioning. However, some clues can be drawn from studies on adolescents and adults with MFS, where physical impairments such as pain, fatigue, aortic dissection and skeletal malformations were reported as negative factors for physical activities, psycho-social development, education, work and family life, [9-15] as well as from studies on children with other chronic and connective tissue diseases, which reported difficulties regarding daily functioning and quality of life. [16-20]

The three objectives of this present qualitative study are to explore parents' perspectives on the impact of MFS on daily functioning of (1) their children with MFS aged 4-12 years, (2) themselves, and (3) their family. These new insights may provide greater awareness of the broad impact of MFS on daily functioning among all professionals involved in the care of children with MFS and their families, and help health care professionals better address patients' support needs.

Methods

Participants and sampling strategy

All participants were parents of a child with MFS aged 4-12 years. Having one or more children with MFS, in a different age group, was no exclusion criteria. Parents for the

individual interviews were recruited from the Amsterdam UMC expert center Marfan syndrome and related (connective tissue) disorders for Children and Youth of the Amsterdam University Medical Centers, Amsterdam, the Netherlands by an invitation letter. They were selected purposively for diversity of gender and parental diagnoses of MFS. This strategy allowed diverse parental perspectives and experiences regarding the impact of MFS on daily functioning to be captured. Saturation of the data was expected after a sample size of 7-10 interviews. This point in data collection, when no new additional data are found that develop new themes, was based on the literature, the complexity of the research question, the interview topic guide and diversity of the sample. [21] Focus group discussions were announced on the Dutch MFS Patient Association website. Parents of a child with MFS age 4-12 could sign up by sending an email. They were not selected purposively.

Interviews and focus groups

To collect data on the same topic, we performed individual semi-structured interviews as well as focus groups. This method was used to assure identified themes and to capture different dimensions of the same topic in order to develop a comprehensive understanding of parents' perspectives on the impact of MFS on daily functioning of their child, themselves and their family. [22] The main framework for a semi-structured conversation for both the interviews and focus groups was a newly developed preset list of open questions based on topics collected from clinical experience and relevant literature [see Table 1]. [9-14, 16-19, 23] A supplementary topic list was provided to obtain more in-depth answers [see Table 1]. We checked for the newly developed preset list of open questions and the supplementary topic list with a parent and a psychologist, expert in qualitative research. These checks did not result in alterations. The semi-structured interviews and two focus groups were conducted by a pediatric rehabilitation physician (JW-K, MD, female). One focus group was conducted by a pediatrician (LM, MD, PhD, female). Both professionals had experience with MFS patient care and were trained in interviewing techniques. The interviews lasted between 30-70 minutes and the focus groups lasted 90 minutes. Fieldnotes were made during and after the interviews and focus groups. Audio recordings were fully transcribed and anonymized.

Table 1. Question guide and topic list for interviews and focus groups

Questions	Topic list (ICF-CY)
What do you know about MFS?	
What does your child know about MFS?	
Which features of MFS does your child have? Which features does your child recognize or mention?	mental functions (b1, s1) sensory functions and pain; vision (b2, s2) voice and speech functions (b3, s3) cardiovascular system, immunological and respiratory functions; fatigue (b4,s4) functions of the digestive, metabolic and endocrine system (b5, s5) genito-urinary functions (b6, s6) neuromusculo-skeletal and movement related body structures and functions (b7, s7) functions of the skin and related structures (b8, s8)
Can you describe the impact of MFS on daily functioning of your child?	learning and applying knowledge (d1) general tasks and demands (d2) communication (d3) mobility (d4) self-care (d5) domestic life (d6) interpersonal interactions and relationships (d7) major life areas: education, school (d8) community, social and civic life: leisure, sport, playing (d9) personal factors: psycho-social development, coping, self-confidence, self-esteem
What kind of physical or emotional support does your child receive?	products and technology (e1) natural environment (e2) support and relationships (e3) services, systems and policies (e5)
What is the attitude of peers and other people towards your child, you and your family?	attitudes (e4)
What are your child's concerns regarding MFS? How is your child's coping, self-esteem and self-confidence?	personal factors
What current and future concerns do you have regarding your child?	physical impairments (b,s) activity limitations (d) participation restrictions (d) environmental factors (e) personal factors
What is the impact of MFS on your own life?	
What is the impact of MFS on your family life?	
Which care or support do you need for your child, yourself and your family?	

ICF-CY, International Classification of Functioning, Disability and Health for Children and Youth. The ICF-CY uses an alphanumeric coding system. The letters used are "b" for Body Function, "s" for Body Structures, "d" for Activities/Participation and "e" for Environmental Factors and are followed by a numeric code that starts with the chapter number of one digit.

Data analysis

A thematic analysis approach was used to analyse the data. [24] Transcripts of the individual interviews and thereafter the transcripts of the focus groups were coded independently and consecutively by 2 of the 3 investigators (JW-K, MD, female; SD, MD, female; AB, PhD, female) using qualitative analysis software (MAXQDA 12 sfqda, 1989-2018, VERBI Software – Consult – Sozialforschung GmbH, Berlin, Germany). [25] Codes concerning children with MFS were linked to the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) categories [23] according to published linking rules. [26] The ICF-CY offers a conceptual framework and a common language and terminology for recording problems manifested in childhood and adolescence involving body functions and structures, activity limitations, participation restrictions, personal and environmental factors important for children and youth. With its emphasis on functioning, the ICF-CY can be used across disciplines (clinicians, educators, policy makers, family members and researchers) to define and document the health, functioning and development of children and youth. [23, 27] The intercoder agreements were calculated in qualitative analysis software [25] and served primarily to improve codes and coding instructions. During the process of data collection, themes were identified and validated in successive interviews until data saturation.

Techniques to enhance the quality of the qualitative data (trustworthiness)

Three investigators (JW-K; SD; AB) ensured the quality of the qualitative research data throughout the data collection and analysis processes. [22] Investigator triangulation, a powerful technique that facilitates credibility (validation) of data through cross verification from two or more sources or researchers was used to ensure rigor. [22] Member checking was performed by asking parents for feedback on the identified and interpreted themes. Expert checking was performed with the members of the Marfan Europe Network during their yearly conference and with members of the board of the Dutch MFS Patient Association. [22] Feedback was added to in the final analysis thereby improving credibility. [22] Standards for Reporting Qualitative Research [28] and Consolidated Criteria for Reporting Qualitative Research [29] assisted during protocol and manuscript preparation.

Results

Participant characteristics

Of the 11 parents approached for consent, 10 participated in an individual semi-structured interview conducted between October 2016 and March 2017 [see Table 2]. One parent did not participate due to a lack of time. Sixteen parents enrolled in focus group meetings at the yearly MFS patient contact day in April 2017. Two parents participated in an interview as well as a focus group [see Table 2].

Table 2. Parent characteristics of individual semi-structured interviews with 10 parents and 3 focus groups with 16 parents (n=5, n=5, n=6)

	Interviews n	Focus groups n
Gender (male/female)	4/6	7/9
Age parents (range) (years)	41 (32-49)	39 (32-55)
Parents with MFS (male/female)	3/2	3/4
Married	9	15
Divorced	1	0
Living together	0	1
Couples (parents of the same child)	2	4
Total children	19	24
Children with MFS	8	16
Age children with MFS (range) (years)	8 (4-12)	8 (2-16)

n, number; no missing data

Interviews and focus groups

All individual semi-structured interviews were conducted at the Amsterdam University Medical Centers. Data saturation was reached after 7 interviews, and no additional material or themes were identified in the 3 successive interviews. Thereafter, enrolment stopped. Then, three focus groups were conducted with parents (n = 5, n = 5 and n = 6).

The intercoder agreement for the interviews was high for code existence and code frequency (mean [range]: 91.4%, [89.3 - 94.2%] and 87.9%, [82.3 - 92.0%], respectively). The intercoder agreement for the focus groups was also high for code existence and code frequency (mean [range]: 81.9%, [80.3 - 83.3%]; 76.0%, [75.4 - 76.4%], respectively). The analysis of the semi-structured interviews identified 2 key themes and 10 subthemes on parents' perspectives on the impact of MFS on daily functioning of children with MFS aged 4-12 years [see Figure 1 and Additional file 1], 2 key themes and 4 subthemes on parents' perspectives on the impact of a child with MFS on parental life [see Additional file 1] and 3 key themes and 2 subthemes on parents' perspectives on the impact of a child with MFS on family life [see Additional file 1]. Thereafter, the analysis of the 3 focus groups verified all identified themes and subthemes and no new themes were identified.

Subsequently, both member and expert checks endorsed all themes, and the expert checks added the importance of acknowledgement of the subtheme: "psycho-social development and behavioural problems in children with MFS". Key themes and

subthemes are presented in Additional file 1, where they are supported by quotes from the parents.

Key themes

Parents' perspectives on the impact of MFS on daily functioning of children with MFS

Cannot keep up with peers

Parents reported that their children could not keep up with peers due to fatigue, pain, physical impairments and experienced participation difficulties in school, sports, play and other leisure activities. Limitations in mobility (sitting, walking, running, throwing balls, carrying and preschool fine motor skills), self-care (dressing and eating) and the deterioration of functional performance over time were addressed. These limitations interfered with their child's participation opportunities.

A mother (interview 9) shared, *"He becomes tired much faster than peers; for example, when he goes shopping, he stops everywhere to rest on benches, on poles, in shops."*

Being different

Parents perceived their child as being different and standing out from their peers due to their physical appearance related to MFS. Clinical features such as tall stature, low body weight, long and slender limbs, arachnodactyly, hypermobility, scoliosis, pectus excavatum and carinatum, pes planus, genu valgum, facial features and supportive devices (splints and wheelchair) were addressed. Due to tall stature, the children' ages were often overestimated, leading to comments and reprimands from adults and peers about "childish and clumsy" behaviour. Furthermore, unsupportive attitudes toward their physical appearance and inability to fully participate in school, sports, play and other leisure activities were addressed.

Regarding tall stature, one father (interview 6) stated, *"Yes, I've been very angry and annoyed by the fact that my child continuously has to hear 'Wow, you are really tall', full of amazement: 'You're really, really, really tall!!!' as if she is a criminal."*

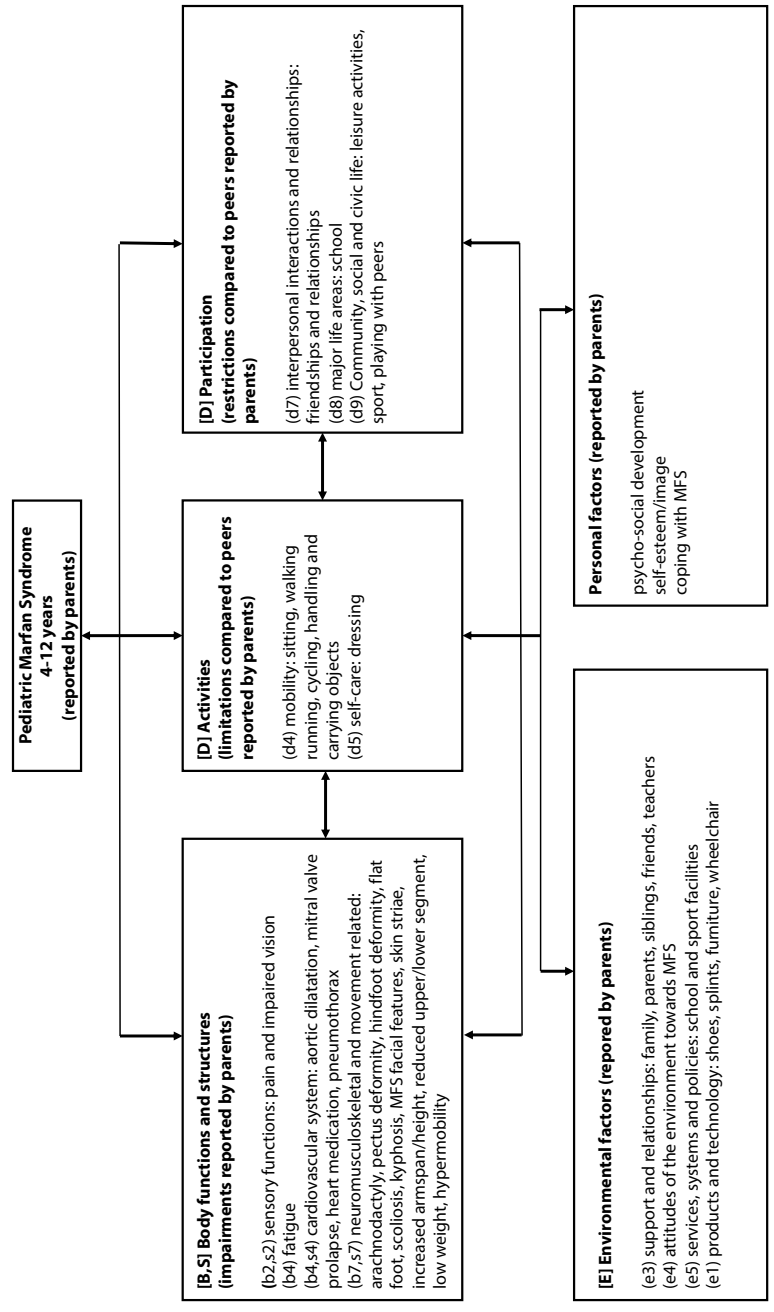

Figure 1: The International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) model: Pediatric Marfan Syndrome 4-12 years; Parents' perspectives of the impact on daily functioning of children with MFS. Parents' meaningful concepts concerning their children with MFS were linked to ICF-CY. The ICF-CY uses an alphanumeric coding system. The letters used are "b" for Body Function, "s" for Body Structures, "d" for Activities/Participation and "e" for Environmental Factors and are followed by a numeric code that starts with the chapter number of one digit.[23,26,27]

Parents' perspectives on the impact of a child with MFS on parental life

Parental burden

Reported parental burden was attributed to multiple sources: high child care needs, lack of professional health care support, a limited social life and parental concerns about their child's physical and psycho-social development.

First, high child care needs and care responsibilities were perceived as stressful. Parents felt highly responsible for their child's health, were sometimes overprotective and feared not being present when something bad happened to their child.

A father (focus group 1, parent 5) reported, *"My greatest fear is that if something goes wrong, I will not be there or I will not anticipate in the right way."*

Second, parents indicated unmet needs for parental support from the health care professionals involved in the care of their child with MFS. They experienced a lack of information about the current and future consequences of MFS on daily functioning of their child with MFS, as well as a lack of transparency in treatments and specialized care to improve their child's daily functioning. Parents reported they felt unprepared for their parental tasks directly after their child was diagnosed with MFS. They indicated a need for tailored support in parental empowerment and access to extended information about the disease-related impact on daily functioning. Moreover, the parents desired professional support in how to discuss the diagnosis and future impact of MFS with their own children and the environment and in dealing with the mental health of siblings and themselves. Furthermore, the parents reported moderate support and understanding from friends and family; when given support, the parents valued it greatly.

Third, the adjusted and complex family schedules, parental duties and high care needs of the child with MFS all resulted in very limited parental leisure time. Consequently, the social life of the parents was limited, which added to the parental burden.

Fourth, future concerns about their child not being able to keep up due to physical deterioration and regular medical check-ups were reported to be stressful. High-risk aortic surgery and early death were feared, especially when family members had already undergone this type of surgery. There were also concerns about standing out from peers because of their child's physical appearance related to MFS, which provoked unsupportive attitudes from peers and adults. Furthermore, concerns about the impact of all this of on the child's psycho-social development, behaviour and coping were indicated.

A mother (focus group 2, parent 8) stated, *"It is actually the emotional, psycho-social part that I am very worried about because she just cannot keep up with peers, and that really makes her sad, and it hurts to see that."*

Financial burden

Because of their children's care needs, the parents regularly took days off from work, took unpaid parental leave, or were employed in a more flexible or less demanding and lower paying job than they were educated for. Additionally, travel expenses due to regular medical visits and higher expenses for clothing and shoes were mentioned.

Parents' perspectives on the impact of a child with MFS on family life

Family burden

The high care needs of a child with MFS and additional care for other family members with MFS strongly affected the organization and health status of the entire family. Familial stress was induced by regular adjustments to complex family schedules. Therefore, family routines, leisure trips and holiday destinations were planned thoughtfully, and cancellations due to health problems experienced by their child with MFS led to great disappointment for all family members.

Regarding this subject, one mother (focus group 2, parent 10) stated, *"In the weekends when we have had a busy day, we need to rest the next day. That is the same problem when we plan our holidays. When we leave for France, we have to drive a day and then rest for a couple of days, otherwise it's not feasible."*

Family cohesiveness and caring

Strong family cohesiveness and caring about family members was perceived as a positive impact of MFS on family life. Family members supported each other with medical issues, concerns, stressful events, and after complicated health problems, they divided tasks and bonded intensely.

Reproductive planning

Reproductive planning discussions between parents and within the family were complicated because of previous experiences. In the focus groups, the parents shared their experiences of their own pregnancies, discusses advances in assisted reproductive technology and discussed the consequences of MFS on the future life of a new-born baby with MFS and on future family life, as well as on the risk of pregnancy for a mother with MFS. Parents indicated their worries about having a new-born who has to live with

the consequences of MFS and indicated the need for more extensive information in order to be able to make reproductive planning decisions. In addition, concerns about the future pregnancy choices of their children with MFS were addressed.

Discussion

This study is the first on parents' perspectives of the large impact of MFS on daily functioning of their child aged 4-12 years with MFS, themselves and their family.

"Cannot keep up with peers" was identified as an important theme in our study. Problems reported in previous studies of adolescents and adults with MFS regarding daily functioning were comparable to those in our parental reports. Adolescents and adults with MFS could not keep up with work, school and sports. Their participation restrictions were caused by pain, fatigue and physical limitations. [3, 5, 9-15, 30] These limitations had a negative impact on their physical and psycho-social development, as well as on their well-being in childhood [3, 5] and adulthood. [9-13] There are also comparable reports on children with various chronic and connective tissue diseases regarding restrictions in daily functioning, reduced quality of life and deterioration of physical performance, as decreased muscle strength, generalized joint hypermobility, increased pain levels, and decreased proprioception and stamina were all associated with decreased physical functioning and participation. [16-20, 31]

"Being different" as a child with MFS and standing out from peers due to physical appearance related to MFS was also an important identified theme. In adults with MFS, unsupportive attitudes and insensitive teasing by peers due to their physical appearance were described and had consequences for their future social behaviour in that they became more introverted and developed a lower self-esteem and self-image. [32] Likewise, a meta-analysis on children with various chronic diseases reported a less positive body image than their healthy peers, [33] which might be a risk factor for lower self-esteem. [34] Another meta-analysis indicated that children and adolescents with visible signs of a disease and appearance-related features of the disease were more likely to be victims of bullying than their healthy peers. [35] Despite these factors, one study showed the quality of life in children and adolescents with MFS was not reduced; however, those children with more distinct physical MFS features (according to the systemic Ghent score [1]) had reduced emotional well-being subscales compared to children with a less distinct physical appearance. [8] A study on adults with MFS also reported a normal quality of life, although patients indicated that their lives would be significantly better without MFS, particularly in the areas of physical activity and self-image. [12] These findings indicate that "being different" due to physical MFS features may affect psycho-social development, self-esteem and behaviour and requires the attention of health care professionals involved in the care of children with MFS.

Parental burden was addressed by the parents in our study. The same holds for parents of children with chronic, congenital heart, and other connective tissue diseases who showed greater parental burden than parents and families of healthy children. [36-41] The sources were comparable: parenting stress and practical problems in daily life, high care child dependency, being chronically ill as a parent, having a limited support system, having a limited social life and having a minimum number of days on holiday. In our study, the parents reported an additional specific source of parental burden: concerns and fear of high-risk aortic surgery and early death, especially when family members had already undergone this type of surgery. The parental assessment of and attitudes towards the children's functioning may be influenced by the parents' fear of an adverse outcome will occur and stress regarding the diagnosis MFS. These concerns were also addressed by the parents of children with a congenital heart disease. Parents generally showed a higher incidence and severity of anger, anxiety, distress, depression, hopelessness and/or somatization symptoms than parents of healthy children. [37]

Furthermore it should be noted that some of the parents are diagnosed with MFS themselves. It may be possible that these parents may extent problems they experience and/or have experienced in their own childhood to their child with MFS. This may cause overprotection and restriction of the child's activities and participation. Therefore it is highly important to inform parents and children about MFS and discuss parental fears and attitudes towards MFS.

Parental burden also affects the family functioning. Families who had fewer psychosocial resources and lower levels of social support were at higher risk of psychological distress and lower family well-being over time. [37, 38] Furthermore, a meta-analysis showed that many dimensions of child well-being, such as problem behaviours, poor social competence and reduced pediatric quality of life, affected family functioning and burden as well. [42] Positive factors such as family cohesiveness and caring for each other reduced parental and family burden, as reported both by parents of children with a congenital heart disease [37, 38] and by the parents in our study.

The parents in our study indicated that they had concerns about reproductive planning and decision making. These concerns have also been reported in parents with children with other HCTD. They indicated that having a child with HCTD significantly influenced reproductive decision-making because of the child's deterioration of health, increased consciousness of reproductive issues and chances in family life after having a child with HCTD. [43, 44]

Study strengths, limitations and further research

The biggest strength of our study is that it is the first to describe the large impact of MFS on daily functioning of children aged 4-12 years, their parents and family. The study was based on qualitative research in which trustworthiness and credibility as well as content saturation and verification were enhanced throughout the entire study period. [22]

Our study has some intrinsic limitations. The focus group participants enrolled themselves without purposive selection for diversity of gender and parental diagnoses of MFS (as we did purposive selection for the interviews). [21] To provide confidence that the identified themes captured all parental perspectives, member and expert checks took place thereafter.

Another limitation is that we used subjective parental observations of Dutch parents with a child with MFS. Questions about the generalizability of our findings to the perspectives of parents from other countries remain present although expert checks [22] with the members of the Marfan Europe Network endorsed all themes. Despite these limitations, we are confident that the qualitative method used and number of interviews and focus group participants were sufficient to identify themes concerning this unexplored research topic.

Our results indicate a need for professional awareness regarding the broad impact of MFS on daily functioning of children with MFS, parents and families. We are convinced that it is crucial for the health care professionals and multi-disciplinary teams involved in the care of children with MFS and their families to be aware of these parental perspectives so they can better understand and address the challenges and support needs of the entire family. Health care professionals should support and empower children to cope with and manage the impact of MFS on daily functioning and to optimize participation in school, sports, and other leisure activities. In this way, children with MFS will be better able to keep up with peers. Professionals should also take into account the impact of a child with MFS on parental and family life and discuss the possibilities of parental counselling and/or psychological interventions for all family members.

Our study and the identified themes on the impact of MFS on daily functioning of children with MFS, parents and families provide direction for future quantitative studies. Surveys on pain, fatigue, functional performance, daily activities, participation, personal factors (behaviour, self-esteem, and self-competence), environmental factors, burden of disease and quality of life in children with MFS are needed. Furthermore, surveys on parental burden and family functioning that investigate and quantify the impact of a child with MFS on parental life and family life are indicated. Then, a core set of objective physical pediatric measurements can be used to observe the clinical and functional outcomes in comparison with subjective reports of parents regarding daily functioning and burden of disease of their children with MFS.

Finally, the parents reported the need for information about the consequences of MFS and the need for interventions to improve daily function of their children, themselves and their family. Hence, individual rehabilitation and education programs may be tailored to empower and improve daily functioning of children with MFS, parents and family.

Conclusion

Parents perceived a large impact of MFS on daily functioning of their children with MFS, themselves and their family. They reported that their children with MFS could not keep up with peers and experienced participation restrictions. Additionally, unsupportive attitudes towards their child's physical appearance related to MFS were addressed. Parental burden was caused by high child care needs, lack of professional health care support, a limited social life and concerns about development. Family burden was caused by adjusted and complex family schedules, other family members with MFS, and reproductive planning decision making. The parents perceived family cohesiveness and caring as positive factors.

More awareness among medical professionals involved in the care of children with MFS, is needed to address and discuss child, parental and family support needs. Then medical professionals can provide tailored interventions, rehabilitation and/or educational programs to empower and improve daily functioning of children with MFS, parents and family.

Acknowledgements

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Additional file 1. Overview of key themes, subthemes/ICF-CY categories supported by quotes from parents: "Marfan syndrome in childhood: Parents' perspectives of the impact on daily functioning of children, parents and family, a qualitative study".

Key themes	Subthemes/ ICF-CY categories	Quotes (Respondent number)
Impact of MFS on daily functioning of children with MFS		
Cannot keep up with peers	school (d8)	• "The school days on which he has to attend school gym are actually the most difficult days for him. On Tuesdays, he starts with school gym, then it is his lunchtime, and then, when his peers go outside to play, he cannot keep up anymore and has to stay inside. School teachers noticed that a full school day is just not feasible for him."(F2P10)
	sports (d9)	• "He does not like football at all because the other kids are just physically stronger and much faster, and then, he is always last to finish." (I2)
	leisure (d9)	• "He often looks a bit lost in the crowd, a bit…, a bit ashamed. For example, at a children's party he stands at a table, and they all want to grab something, then the other children are always first." (F3P12)
	play with peers (d9)	• "When she comes home, she tells about her girlfriends who can run faster, and if they play tag, she will not manage to tap someone because she is not fast enough." (F3P16)
	fatigue (b4)	• "We can undertake something together for half a day, but a full day is not feasible, and if we try a full busy day, then he gets overtired and has to throw up in the evening; that is really intense." (F1P2)
	pain (b2)	• "She has 'the joint MFS', so her joints cause problems and pain. We are not able to go out for a full day, for example, if we go for a walk, after an hour she says: 'Mom, I suffer from my back and knees, and I am tired.' So, I experience that she is always in pain, and no, she does not complain but I see she suffers. And, then, I worry there is nothing to do about this pain, yes, pain medication, but I prefer not to give that to her because she is still so young. Then, professionals tell me, the heart is still not too bad….. but she is in pain all day." (F3P15)
	mobility (d4)	• "She is a little less fast and a bit clumsier than her friends. And, then, children in our neighborhood laugh at her when they are having cycling and running games together." (F2P9)

Additional file 1. Continued

	self-care (d5)	• "Tying his shoes takes a long time. We always have to wait for my son, so we are used to that now. At least he does it all by himself. And buttons…, that does not work well, for example, he has not enough strength to press buttons." (I4)
Being different	personal factors	• "We noticed that she is starting to become a bit more insecure about certain things, such as her tall stature. She is now slowly getting aware of her body. She starts asking us questions from time to time, or becomes sad: 'I'm pretty tall, and how is that possible, and why do I not look like my girlfriends?' So, her physical awareness slowly starts, and that worries me."(I7)
	unsupportive attitudes (e)	• "When she is on her knees, she needs 5 minutes to get up like an old woman, and then, there are children who say ugly things and laugh at her." (F3P15)
Impact of a child with MFS on parental life		
Parental burden	concerns	• "I especially notice an increase in fatigue, and I worry about how much energy he needs, to be able to do his schoolwork. What will his energy level be at high school; can he really handle it, or should he take a step back? We will see."(F2O10)
	lack of support	• "He is the first MFS patient in our family, and then, my family starts asking questions like: 'Is he not too thin?' and 'Please give him food!' I think children with MFS are already very thin and tall, and those remarks are not supportive for his self-confidence either, but how do I explain that to my parents and aunts? " (I4)
	care needs	• "He needs a lot of care, and those therapies and appointments are always planned during school hours, never after. That is definitely not convenient, but it seems as if doctors always think that you, as a parent, just have all the time in the world." (I3)
	limited social life	• "I think I really have to take into account my child's energy level as well as the energy level of my partner with MFS, who also has limited energy. For example, today we're going to the hospital and tomorrow I will have to keep my children busy on my own because my partner has to rest; yes, I have a very busy life."(I2)
Financial burden		• "Sometimes it is a lot of hassle, all arrangements. And, at work, my colleagues say: 'Do you really have to take a day off to go to the hospital with your child…again?' I find that the hardest. Even though I arrange everything, I have to explain continuously. She has MFS, and no, I cannot arrange it any differently because those doctors only work on a certain day. Coincidentally, I also work on that day." (I7)

Additional file 1. Continued

Impact of a child with MFS on family life		
Family burden	family schedules	• "It affects our family activities because we are not able to do a lot of things because our son is tired quickly and cannot walk or cycle far distances."(I9)
	other family members with MFS	• "I'm worried about the fact that there is a chance that he will not survive sooner or later, and that's what I'm worried about, that his sister by then is actually the only one left, and of course, I do not know what will happen to my own health. How long will I survive, and I'm worried that maybe in the future only mother and daughter remain, but you know when you are diagnosed with MFS, there's just a chance that something will go terribly wrong, especially with the heart." (I1)
Family cohesiveness and caring		• "Our family slogan is always: 'We know that we are special and that we are good at things and less good at other things, and that we have to take care of each other, and we do so.'(F2P7)
Reproductive planning and decision-making		• "I was done with pregnancies after we (my son and I) were diagnosed with MFS; I really do not want to pass on this disease to another child." (I8)

ICF-CY, International Classification of Functioning, Disability and Health for Children and Youth. The ICF-CY uses an alphanumeric coding system. The letters used are "b" for Body Function, "s" for Body Structures, "d" for Activities/Participation and "e" for Environmental Factors and are followed by a numeric code that starts with the chapter number of one digit. I, interview; F, focus group; P, parent; MFS, Marfan syndrome.

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CHAPTER 3

"Me and my favorite sport swimming" by Eva Weesink (17 years)

Marfan syndrome in adolescence: Adolescents' perspectives on (physical) functioning, disability contextual factors and support needs

Warnink-Kavelaars J, Beelen A, Goedhart T, de Koning LE, Nollet F, Alsem MW, Menke LA, Engelbert RHH. *Eur J Pediatr*. 2019;178(12):1883-1892. doi:10.1007/s00431-019-03469-7

Abstract

Background Although essential for providing optimal adolescent patient support, knowledge of the impact of Marfan syndrome in adolescence is limited.

Methods To explore adolescents' perceived impact of Marfan syndrome on (physical) functioning (activities, participation), disability (limitations, restrictions), contextual factors and support needs, we interviewed 19 adolescents with Marfan syndrome. Audio-recordings were transcribed, coded and analysed using thematic analysis.

Results Identified themes were "difficulties in keeping up with peers" and "being and feeling different from peers". Furthermore, an adolescent Marfan syndrome -specific International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) model derived from the data describing the adolescent perceived impact of Marfan syndrome on functioning, disability and its contextual factors. Adolescents perceived problems in keeping up with peers in school, sports, leisure, friendships/ relationships and they could not meet work requirements. Moreover, participants perceived to differ from peers due to their appearance and disability. Contextual factors: coping with Marfan syndrome, self-esteem/image, knowledge about Marfan syndrome, support from family/friends/teachers, ability to express needs and peer-group acceptation, acted individually as barrier or facilitator for identified themes.

Conclusions Adolescents with Marfan syndrome perceived limitations and restrictions in (physical) functioning. They perceived problems in keeping up with peers and perceived to differ from peers due to their appearance and disability. This warrants awareness and tailored physical, psychosocial, educational and environmental support programmes to improve (physical) functioning and empowerment of adolescents with Marfan syndrome.

Introduction

Marfan syndrome (MFS) is a rare Heritable Connective Tissue Disorder (HCTD) caused by a mutation in the *FBN1*. The incidence is approximately 2-3 in 10000 worldwide. [1] Manifestations of MFS in body structures and functions are well described and the MFS diagnosis relies on defined clinical criteria (revised Ghent nosology). [1] A markedly variable phenotype can be present in MFS and a different number of disabilities can appear, even in the same family. [1-6]

Although essential for providing optimal adolescent patient support, studies on the overall impact of MFS on (physical) functioning (activities, participation), disability (limitations, restriction) and contextual factors during adolescence are sparse.

Current studies reported significant burden on physical activities, [3, 7-9] schooling and job opportunities, [10] low work participation [11] and self-image [9] in adolescents and young adults with MFS. Then a review showed that MFS had a significant impact on psychosocial aspects: decreased quality of life, education, work and family life, depression and anxiety. [12] Moreover our recent qualitative study in parents on the perceived impact of MFS on daily functioning of their children aged 4-12 years with MFS showed that their children with MFS could not keep up with peers and experienced participation restrictions and unsupportive attitudes towards their physical appearance related to MFS. [13]

Furthermore, studies on (physical) functioning of children and adolescents with related congenital heart and connective tissue diseases showed the limiting impact of disease-related physical problems on physical activities [14-16] and the negative impact on school attendance and extracurricular activities, [14] play and leisure, [17] and school participation. [18] Moreover MFS and cardiovascular diseases guidelines gave some advice on physical activity and sport participation. [19] Current literature showed limited knowledge of the impact of (MFS) in adolescence.

The first aim of this qualitative study is to explore adolescents' perceived impact of MFS on (physical) functioning (activities, participation), disability (limitations, restrictions), contextual factors and support needs. The second aim is to develop an adolescent MFS International Classification of Functioning Disability and Health for Children and Youth (ICF-CY) model describing the impact of MFS on adolescents (physical) functioning and disability. The indicated themes and the adolescent MFS-specific ICF-CY model may improve communication and awareness of the adolescent's perceived impact of MFS by medical staff and related health professionals, the adolescents with MFS themselves and their relatives and friends that could prevent under-recognition and under-treatment. This requires individually tailored physical, psychosocial, educational and environmental

support programmes to improve (physical) functioning and empowerment of adolescents with MFS.

Materials and methods

Participants and sampling strategy

The Medical Ethics Review Committee of the Amsterdam University Medical Centers, in the Netherlands has waived ethical approval under Dutch Law (reference number W17_054#17.071). Adolescents with MFS aged 12-18 years, treated at the Amsterdam University Medical Centers, were recruited by letter and selected for diversity of age and gender. [20] Participation in this study was voluntary and written informed consent was obtained from all participants.

Interviews

The main interview framework was a newly developed question guide for semi-structured interviews [see Table 1] based on topics collected from relevant studies on MFS and other connective tissue and related disorders, clinical experiences and remarks from Dutch and European MFS patient associations. This list was checked by a psychologist (qualitative research expert); no alterations were made. Data saturation was expected after a sample size of 14-18 interviews. [20] This point in data collection, when no new additional data for new themes were found, was based on the literature, the complexity of the research question and the diversity of the sample. Field notes were made. Adolescents could choose an interview with a pediatric rehabilitation physician (JW-K, MD, female) alone or in the presence of their parents. Parents were asked not to interfere.

Data analysis

Data were analysed with a thematic analysis approach. [21] Audio-recordings were transcribed, and concepts were coded by two investigators (JW-K, MD, female; TG, MD, female) using qualitative analysis software (MAXQDA 12 sfqda, 1989-2018, VERBI Software – Consult – Sozialforschung GmbH, Berlin, Germany). During the process of data collection, identified codes were validated in successive interviews until saturation was reached. [20] The calculated intercoder agreements served primarily to improve codes and coding instructions. Codes were structured to the domains of the ICF-CY, [22] which offers a conceptual model for recording problems manifested in childhood and adolescence involving body functions and structures, activity limitations, participation restrictions and contextual factors. Themes were identified as well as contextual factors acting as a barrier or facilitator for identified. The adolescents' reported support needs were categorised.

Table 1. Question guide for semi-structured interviews

Question guide for semi-structured interviews
What do you know about MFS?
How did you gather this information?
Which features of MFS do you have yourself?
What is the impact of MFS on your activities?
What is the impact of MFS on your participation in daily life?
What are your concerns about your daily life (related to MFS)?
How do you manage and cope with your limitations, restrictions and concerns (related to MFS)?
What kind of physical or emotional support do you get and what helps you to participate in daily life?
Who and how did you tell about MFS?
What is the attitude of peers and other people towards your disease?
What is the impact of MFS on your family life?
Have you thoughts about your future adult life (work, relationships, family life, health, leisure)?
Which supplementary (medical) support do you need and what is your advice to optimise adolescent MFS care?

Strategies to ensure trustworthiness and credibility

Three investigators (JW-K, MD, female; TG, MD female; AB, PhD, female) ensured trustworthiness and credibility throughout the data collection and analysis process. [23] Investigator triangulation was used to ensure rigour. [23] The manuscript reporting adheres to consolidated criteria for reporting qualitative research (COREQ), guidelines for reporting qualitative studies and the Standards for Reporting Qualitative Research. [24, 25]

Results

Participant characteristics

Of the 21 adolescents with MFS approached to participate in the study, 2 declined, 1 due to lack of time and 1 gave no specific reason. All 19 adolescents gave written informed consent and were interviewed between March 2017 and March 2018. In all participants a pathogenic *FBN-1* variant was confirmed. Parents of 15 adolescents were diagnosed with MFS [see Table 2].

Table 2. Participants' characteristics

Total participants	**19**
Gender (male/female)	12/7
Age (range) (years)	14.5 (12-17)
Confirmed pathogenic FBN1 variant	19
Participant with parent with MFS	15
Ectopia lentis	9
Z score > 3 aortic root dilatation	4
Mitral valve prolaps	9
Heart medication	11
Systemic Ghent score ≥ 7	10
Beighton ≥ 6	10
Aorta operation	1
Lens operation	2
Foot operation	1
Secondary education level : (low vocational /middle vocational / higher general/ pre-university education)	0/5/6/8

No missing data

Interviews

All 19 interviews were conducted at Amsterdam University Medical Centers; 7 with the adolescent alone, 10 in the presence of one parent, and 2 in the presence of both parents. The interviews lasted between 30-75 minutes. Data saturation was reached after 14 interviews; no additional codes were identified in 5 successive interviews. After that, enrolment stopped. The intercoder agreement for the interviews was high for code existence and code frequency (mean [range]: 85.9%, [77.5 - 91.1%] and 81.0%, [71.3 - 87.8%], respectively).

Themes

Identified themes related to (physical) functioning and disability were "difficulties in keeping up with peers" and "being and feeling different from peers" [see Table 3 and Figure 1].

Difficulties in keeping up with peers

"I really notice that I am not always able to participate. In sports, in particular, I often have to give up earlier. My knees ache a lot; so many times I stop before we're done." A8

Adolescents perceived problems in keeping up and participating with peers in school, sports, leisure, friendships/relationships and they could not meet work requirements. Time-consuming medical visits and treatments made it more difficult to participate in activities with peers.

School: Adolescents perceived difficulties in continuing a full school day, completing their school assignments, participation in gymnastics and leisure. This limiting impact of pain, fatigue, medical visits and treatment appointments on their pace of schoolwork was hardly taken into account by their teachers.

Sports: Adolescents reported they could not keep up with their peers during sports due to physical impairments and limitations in physical activities. Fear of increased musculoskeletal injuries, pain and fatigue, aorta and eye problems were mentioned. Alternatively, adolescents focused on individualised sports or implemented a physical activity in their schedule.

Leisure: Leisure activities such as (visits to) parties, theme parks, concerts and holidays were perceived as too exhausting; they often cancelled. Adolescents tried to find achievable leisure activities to participate in with peers.

Friendships/relationships: Maintaining friendships was perceived as complicated. Accompanying friends to (physical) activities, such as meeting at sport clubs, hiking or shopping was not always feasible due to fatigue and pain. Adolescents also addressed difficulties in making new friends, and reported feeling insecure about themselves. Out of 19 adolescents with MFS, two were into a relationship, both with a healthy partner. Adolescents responded that they had not met the right person yet or had no time for dating.

Work: Adolescents reported they could not meet the same work requirements as their peers. Working in a supermarket, restaurant, bar or shop was physically demanding because of regular carrying and/or lifting. Long hours standing and walking were considered challenging because of increased pain and fatigue. Adolescents selected physically less-demanding jobs such as teaching younger students.

Being and feeling different from peers

"It bothers me sometimes, being an exception. I am insecure because you can see that we are very tall or very thin, and people will notice the dent in my chest, and ask me "what's wrong with you?"; It's not always nice, having to tell them you have Marfan's, and I have to keep telling them over and over." A4

Appearance: Adolescents described themselves as different from their peers due to their appearance, fatigue and pain problems. They described their appearance as different..

Disability: Adolescents perceived limitations in activities compared to peers. They reported limitations in mobility; household tasks and physical/sport activities compared to peers. These limitations were variable among adolescents and depended on the severity of physical impairments, pain and fatigue.

Feeling different from peers: Adolescents indicated feeling different from peers because of their MFS appearance and disability. Bullying enhanced their negative feelings about themselves and their peer status. Some adolescents reported a negative self-image/ esteem and consequently avoided social activities such as going to the swimming pool, beach, parties or sports activities.

Contextual factors

Adolescents reported environmental and personal factors acting variably as a barrier or facilitator on the identified themes [see Table 3].

Coping with MFS: Adolescents reported positive and negative coping strategies to handle the impact of MFS on their (physical) functioning and disability. The reported positive coping styles, which seemed to improve their functioning, were pro-active coping, seeking social support, having a humorous and relaxed outlook on life, reappraising the disease and their disability in a positive light, acceptation and a healthy lifestyle. Most adolescents anticipated and planned their lives within their physical abilities to improve their participation in school, sports, leisure and work. Most adolescents sought social support from parents, friends and teachers, and most adolescents showed a humorous and relaxed outlook on their lives and did not worry much about medical issues. Some adolescents reassessed their negative associations about their MFS appearance and reported their tall stature as a benefit in sports like basketball and in getting into pubs at an early age. Adolescents reported better self-image and acceptation of their disability when they got older. Most adolescents were aware of the importance of a healthy lifestyle and incorporated physical activities in their weekly schedules.

Reported negative coping styles were avoidance and denial. Some adolescents avoided social activities with peers because they could not keep up or because of their low self-image. Furthermore, some adolescents did not want to know about MFS and future consequences.

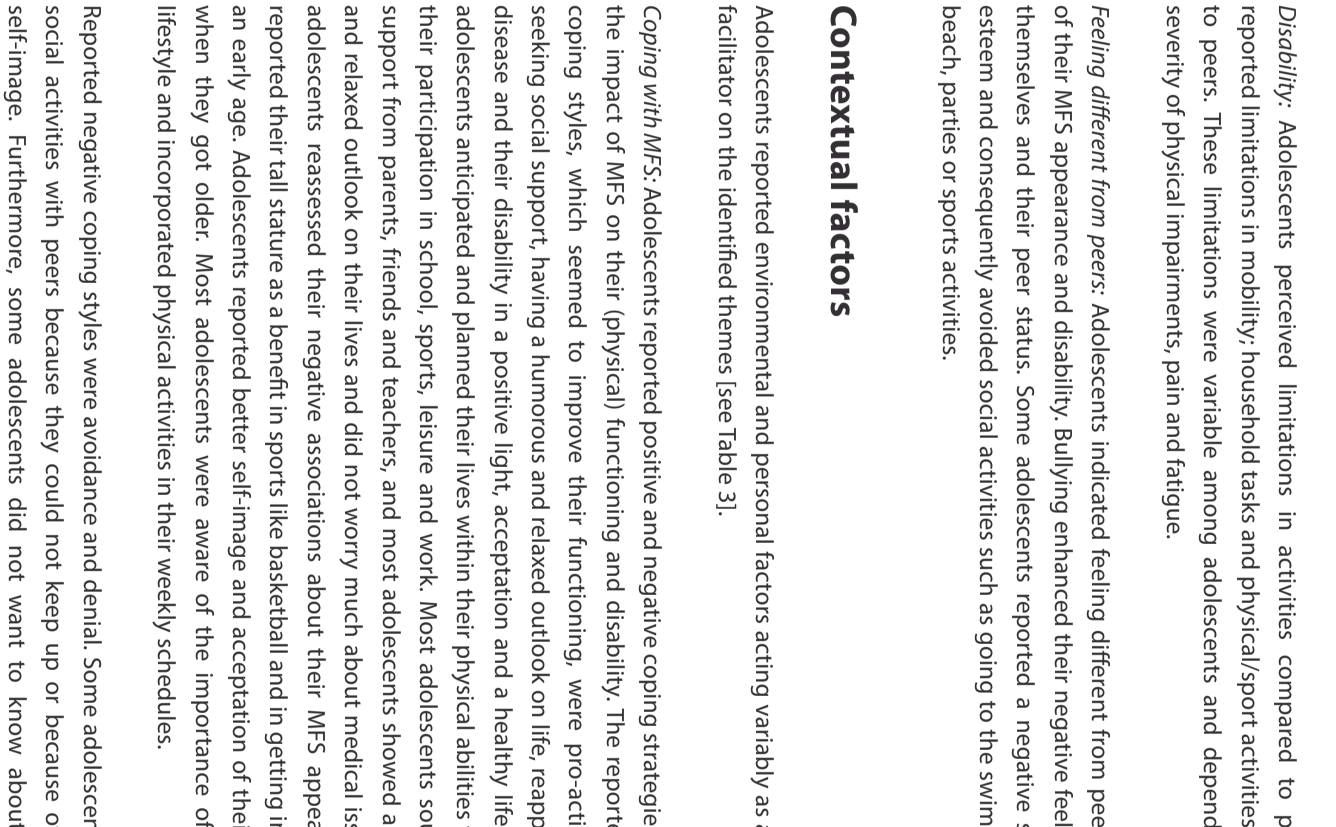

Figure 1. Adolescent Marfan syndrome-specific International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) model derived from the data describing the adolescent perceived impact of Marfan syndrome on (physical) functioning, disability and its contextual factors. The ICF-CY uses an alphanumeric coding system. The letters are according to the ICF-CY: "B" for Body Function, "S" for Body Structures, "D" for Activities/Participation and "E" for Environmental Factors and are followed by a numeric code that starts with the chapter number of one digit. [22]

Table 3. Overview of themes on the impact of MFS on functioning, disability and contextual factors acting as a barrier or facilitator supported by the data: quotes from adolescents with MFS aged 12-18 years.

Themes		Quotes
Difficulties in keeping up with peers	school	• "Yes, Marfan's does take up a part of my life, because I have to go to the hospital very often, for appointments and other things. I try to schedule my visits to the hospital so they don't conflict with school, and I don't have to miss any classes, but that is difficult. It is usually very busy at the hospital, and the appointments have to take place during school hours. This means I miss many classes. And I cannot participate in a lot of activities during Phys-ed." A6
	sports	• "I really notice that I am not always able to participate. In sports, in particular, I often have to give up earlier. My knees ache a lot, so many times I stop before we're done." A8
	leisure	• "I had problems last year; we went to Disneyland in Paris, and I was exhausted after only an hour and a half. At the time, my back, ankles and knees were really bothering me." A13
	friendships/ relationships	• "Well most of the time I am too tired to meet with friends after school and then, at home, I sit down on the couch to relax. So I don't really have time to meet with someone, that's hard, but I usually play a game on my phone or I play online games together with friends. "A8
	work	• "At first, I had a part-time job at the local drugstore, stocking shelves, but I had to quit because my back was causing a lot of pain. So, I had to make a decision. I mean, it is a shame, because it was nice to earn some money, but my health is my main priority." A5
Being and feeling different from peers	appearance	• "I am taller and thinner than the other kids in my class, and I have spider hands." A10
	fatigue	• "I went to a concert with some of my friends, and I was really very tired. I was thinking "this isn't right," but on the other hand, I realized that I had had a really good day, so..." A2
	pain	• "Yes, the pain makes me unable to bend my hand fully. I can now, but I was not able to do it yesterday, and usually, it stays that way for a couple of days. I don't know if I strained it, or if it is caused by too little connective tissue, but when it happens, I really have a lot of pain in my wrist. I often drop my phone, I just lose my grip on it." A1
	activities	• "I have an elevator pass that allows me to use the elevator, because taking the stairs is too hard, and I have a second set of books, so I don't have to carry them from home to school. The second set is kept at school, in my locker, so my bag is lighter. It prevents me from having to lift things, and keeps me from getting tired so quickly." A3 • "I am able to clean my room or do things like that, but when we go grocery shopping, my mother will tell me I don't have to carry the heavy items because I can't." A12
	feeling different	• "It bothers me sometimes, being an exception. I am insecure because you can see that we are very tall or very thin, and people will notice the dent in my chest, and ask me "what's wrong with you?"; It's not always nice, having to tell them you have Marfan's, and I have to keep telling them over and over." A4

Table 3. Continued

Contextual factors acting as a barrier or facilitator		Quotes
Coping with MFS	acceptation	• "In the beginning, when I was younger, I had a hard time dealing with the fact that I have Marfan's. But then I accepted the fact that I have an illness, and this is here to stay for the rest of my life, it isn't going to change or anything. So accepting it really helped, and nowadays it's no longer a problem for me." A6
	humorous and relaxed outlook on life	• "Yes, I was disappointed when I had to give up basketball (highest junior league) because of Marfan's because I really liked playing. But it's in my character to try and make the best of the situation. So yes, now I am going to try to become as good as I can in my music." A10
	pro-active/ planning	• "I plan a lot in advance. For instance, if I know there are four tests (at school), I start preparing early, so I have less to do each day, and not two whole paragraphs on one day. That is too exhausting, and I get a headache if I do too much." A18
	avoidance and denial	• "I really don't want to have anything to do with Marfan's. I quickly go to the hospital, and that's it for me." A7
Self-esteem/image		• "When I went swimming, people would react to my chest, saying things like "look at that" and other things. Yes, it bothered me a lot, and it prevented me from going sometimes. I would think "I really can't deal with this now" and not go." A5
MFS knowledge		• I know you get thinner when you have Marfan's, you can break bones easier, and your eyes can be more sensitive. And yes, your aorta also grows, or something. Other than that, I don't really know all that much about it." A19
Ability to express needs		• "If something happens to me, I think I would like to be able to talk to someone who also has Marfan's and who has experienced the same thing." A15
Support and peer group acceptance	friends	• "Yes, I have explained what Marfan's is to my friends, so they understand it completely, and they are considerate. One of them actually just sent me a message, wishing me good luck today." A14
	parents	• "Yes, when I am worried, I can talk to my sister, and to my parents." A18
	teachers/ school	• "I was unable to take the stairs or to keep up with the rest during the Phys-ed classes. I also had trouble studying, because there were too many stimuli at school, and after school, I was so tired, so basically, I just slept a lot. And I always had too little time to study or to do my homework. Now, at my new school, they understand that I have Marfan's, and I get a lot of guidance and support. I am doing a lot better now." A13

MFS, Marfan syndrome

Self-image/esteem: Adolescents reported that acceptance of their appearance helped them to feel accepted and less different from peers. Shame about appearance and fear of bullying acted as barriers for participation in social activities with peers.

Knowledge and future thoughts on MFS: Adolescents indicated that their knowledge of MFS was limited. In-depth questioning revealed knowledge about the development of physical impairments, (physical) functioning and disability and thoughts about a possible negative impact of MFS on school, sports, work, friendships and relationships and of their future offspring. Adolescents were mostly informed by their family, some of whom were diagnosed with MFS, and by medical professionals. The internet, other adolescents with MFS or the MFS patient support group were sometimes consulted. Most adolescents had limiting thoughts about their future, related to MFS or in general. Those with family members with complicated health problems due to MFS reported more awareness.

Ability to express support needs: In general, adolescents were satisfied with the current MFS (medical) support. They had difficulties expressing their support needs because they did not exactly know what type of support is available, but ultimately were able to state several support needs [see Table 4].

Support from parents, friends and school: All adolescents reported that support from family, friends, teachers, medical staff and related health professionals facilitated participation in school, sports, leisure, chores, work and friendships/relationships Families took into account the MFS-related limitations and restrictions in scheduling and planning leisure time and holidays, and stimulated adolescents to participate in activities with peers. Adolescents also perceived support from friends, such as texting during medical check-ups or invitations for (physically) achievable activities. Some teachers and employers provided excellent support and facilitated customised school programmes and work activities. On the other hand, some adolescents perceived little or no support from friends and teachers, which acted as a barrier to participate in school, sports and peer activities.

Peer group acceptance: Adolescents reported having best friends in school and their environment that made them feel accepted. Nevertheless, most adolescents reported the feeling of standing out from their peers because they could not always keep up with their peer group. They also reported bullying about their MFS appearance and/or limitations and restrictions in their (physical) functioning. Adolescents reported to stay quiet about their disease, in order to be accepted by their peers, although some would inform classmates about their disease, (physical) functioning and disability.

Table 4. Adolescents' reported support needs

Adolescents' reported support needs. They asked for advise on:
(1) improvement of fatigue, pain and physical impairments
(2) improvement of physical and sports activities
(3) pro-active planning of school and other activities
(4) safe and fitting sports activities
(5) fitting temporarily site-jobs
(6) fitting higher education
(7) future work possibilities
(8) organizing feasible social activities with peers
(9) support programmes on self-esteem and body image
(10) a healthy diet to gain weight
(11) writing material/typing
(12) furniture, clothing, shoes and splints
(13) easy access to websites and educational programmes about MFS for themselves and for their families, friends and teachers
(14) contact groups with other adolescents with MFS

MFS, Marfan syndrome

Discussion

This qualitative study showed that adolescents with MFS perceived limitations and restrictions in (physical) functioning. Indicated specific themes were (1) difficulties in keeping up with peers and (2) being and feeling different from peers due to their appearance and disability. Furthermore, an adolescent MFS-specific ICF-CY model of (physical) functioning and disability with its contextual factors acting as a barrier of facilitator derived from the data and adolescent support needs were categorized.

Themes

The theme "difficulties in keeping up with peers" we identified is supported by earlier studies of adolescents and young adults with MFS who reported significant burden on schooling and job opportunities [10] and low work participation. [11] Also in adolescents and children with related congenital heart and connective tissue diseases, the negative impact of disease on school attendance and extracurricular activities, [14] play, leisure [17] and school participation [18] were reported. Our study data add restrictions for higher education, work, sports, leisure and friendships/relationships in adolescents with MFS. Therefore, we recommend addressing these topics during counselling.

The other theme "being and feeling different from peers" we identified is in line with studies in adolescents with MFS that reported limitations in physical activities [7-9] and self-image. [9] One systemic review concluded a significant impact of MFS on psychosocial aspects in adults: decreased quality of life, challenges in education, work and family life, depression and anxiety. [12] Furthermore a correlation was found between perceived discrimination or socially devaluation because of having MFS and depressive symptoms, low self-esteem, physical impairments and perceived workplace discrimination. [26] Since being and feeling different from peers hinders (physical) functioning, we advise to discuss this subject with each adolescent with MFS.

Adolescent MFS-specific ICF-CY model and contextual factors

An adolescent MFS-specific ICF-CY model derived from the data describing the adolescent perceived impact of MFS on (physical) functioning, disability and its contextual factors. Our participants reported support of parents, friends and teachers as a facilitator to participation with peers. A systematic review also concluded that support and positive relationships with peers contributed significantly to the participation of adolescents with congenital or acquired disorders. [27] Moreover, support of family helped adolescents with congenital heart disease to adopt a positive perception toward participation in activities. [28] Therefore, parents, friends and family should be made aware of the positive effect of support on (physical) functioning.

Our study shows that the contextual factor "knowledge about MFS" was limited in our participants, which could explain the limiting thoughts about their future life with MFS and the difficulties they had in expressing their support needs. A study on children and adolescents with chronic heart disease, [29, 30] asthma and epilepsy [31] also showed knowledge gaps. Education about appearance, functioning and disability of MFS might help as a positive coping strategy and stimulate discussions about the adolescent (physical) functioning, which in turn may improve their ability to formulate support needs. This is supported by a study on adults with MFS that reported education on MFS as a positive coping strategy. [26]

Functioning versus quality of life and life satisfaction

Although quality of life and life satisfaction are different constructs, they might relate to functioning and disability. Children and adolescents with MFS have, like adults with MFS, [32-34] a high risk of impaired health-related quality of life. [35] One study reported an unimpaired quality of life in adolescents [36] despite the distinctive phenotype, but children with symptoms related to the systemic Ghent score had a reduced quality of life and sub-scale scores on emotional well-being, compared to unaffected patients with MFS. The relationship between functioning and disability, quality of life and life satisfaction is worth investigating. [37]

Study strength and limitations

The strength of our qualitative study is that it is the first to describe adolescents' perspectives on the impact of MFS on (physical) functioning, disability, contextual factors and support needs, which is not frequently addressed in the literature. The trustworthiness, credibility, content saturation and verification of this study were guaranteed throughout the entire study period.

Our study has some limitations. First, adolescents were not sent a resume of their interview. Second, all participants had the Dutch nationality and were treated in the Amsterdam University Medical Centers, expert center Marfan syndrome and related disorders. Nevertheless, we assume that the results apply to adolescents with MFS and provide insights into assessments in other countries to observe intercultural differences.

Clinical implications and further research

Our qualitative study contributed to themes on (physical) functioning and disability important to adolescents with MFS and to a complete overview of the adolescent's perceived impact of MFS on (physical) functioning and disability. These themes and the adolescent MFS-specific ICF-CY model may be helpful in communication with the adolescents, relatives and medical staff as well as related health professionals about keeping up with peers, perceived being and feeling different from peers, and their (physical) functioning and disability. The adolescent MFS-specific ICF-CY model will also help identify (physical) functioning and disability within the acting contextual factors (barrier or facilitator) in the individual adolescent with MFS. We recommend a needs assessment and individual counselling on (physical) functioning, disability, contextual factors and support needs for every adolescent with MFS. This could prevent current and future disability.

The data from this study will be used to compile a core set of surveys and physical measurements regarding (physical) functioning and disability. With the knowledge obtained from these assessments, we aim to get qualitative and quantitative determinants of (physical) functioning and disability as well as acting contextual factors. This will enable us to develop customised physical, psychosocial, educational and environmental support programs to improve (physical) functioning, empower adolescents with MFS and improve MFS health care.

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CHAPTER 4

"Me and my best friends" by Merel van der Linden (12 years)

Parenting a child with Marfan syndrome: Distress and everyday problems

Warnink-Kavelaars J, van Oers HA, Haverman L, Buizer AI, Alsem MW, Engelbert RHH, Menke LA. (2021). *Am J Med Genet A*. 2021;185(1):50-59. doi:10.1002/ajmg.a.61906

Abstract

Background Marfan syndrome (MFS) is a multisystemic, autosomal dominant connective tissue disorder that occurs de novo in 25%. In many families, parent and child(ren) are affected, which may increase distress in parents.

Methods To assess distress, 42 mothers (29% MFS) and 25 fathers (60% MFS) of 43 affected children, completed the validated screening-questionnaire Distress thermometer for Parents of a chronically ill child, including questions on overall distress (score 0-10; ≥ 4 denoting 'clinical distress') and everyday problems (score 0-36). Data were compared to 1134 control-group-parents of healthy children.

Results Mothers reported significantly less overall distress (2, 1-4 vs. 3, 1-6; p = .049; r = -.07) and total everyday problems (3, 0-6 vs. 4, 1-8; p = .03; r = -.08) compared to control-group mothers. Mothers without MFS reported significantly less overall distress compared to mothers with MFS, both of a child with MFS (1, 0-4 vs. 3.5, 2-5; p = .039; r = -.17). No significant differences were found between the father-groups, nor between the group of healthy parents of an affected child living together with an affected partner compared to control-group parents. No differences in percentages of clinical distress were reported between mothers and control-group mothers (33% vs. 42%); fathers and control-group fathers (28% vs. 32%); nor between the other groups. Distress was not associated with the children's MFS characteristics.

Conclusions Parents of a child with MFS did not show more clinical distress compared to parents of healthy children. However, clinical distress was reported in approximately one-third and may increase in case of acute medical complications. We advise monitoring distress in parents of a child with MFS to provide targeted support.

Introduction

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder caused by a pathogenic variant in *FBN1* [1] and occurs de novo in a quarter of patients. In many families, both a parent and one or more children are diagnosed with MFS. The estimated prevalence is 1:5.000-1:10.000 [2] and the diagnosis is based on the revised Ghent criteria. [1] Children and adults/parents with MFS need regular medical follow-up [3-5] because of the risk of developing medical complications of the cardiovascular- (aortic aneurysm, mitral valve prolapse), musculoskeletal- and ophthalmic- (ectopia lentis, severe myopia) systems. [1, 2, 6-10] Therefore, parents may have extended caregiving responsibilities, both for their child/children with MFS and for themselves or their partner with MFS, which may further increase distress and everyday problems.

In a recent study, we found that parents of a child with MFS reported parental burden caused by high parental caring requirements for their child's medical and psychosocial needs, lack of professional health care support, a limited social life, parental concerns about their child's physical, psychosocial development and fear of high-risk aortic surgery or early death. [11] Also, in parents of children with other chronic illnesses, parental functioning was negatively affected [12] as well as their participation. [13] Parents suffered from anxiety and depression, [14] parenting stress [15] and parental burden. [16-18] Moreover, parents of a child with cancer, [19] home parenteral nutrition, [20] mucopolysaccharidosis type III, [21] inflammatory bowel disease, [22] Down syndrome [23] and a chronic disease of any type, [24] screened by the Distress thermometer for Parents of a chronically ill child (DT-P), [25, 26] reported significantly higher distress and/or more often everyday problems compared to control-group parents. These and other studies also reported significant differences in distress levels of mothers compared to fathers. [14, 19-21, 23, 27] There is limited knowledge of the distress of parents who have a chronic illness themselves. Some studies reported the adverse effects of chronic illness on parental health-related quality of life [13, 28] and a tendency of limited social and family activities for all family members. [29] Studies on distress in parents and parenting a child with a chronic or connective tissue disorder while being affected by the same disorder; as well as studies on distress in healthy parents and caring for an affected partner and an affected child, are even rarer. However, studies reporting on the health-related effects of MFS in adults on family life, physical activities, psychosocial development, education, work, and reproductive planning provide clues for understanding distress in parents with MFS. [9, 10, 30-36]

This study aims to assess distress and everyday problems of mothers and fathers without and with MFS, of a child with MFS using the DT-P. Data are compared to those of control-group mothers and fathers of a healthy child. Associations will be explored between distress in parents and the presence of MFS characteristics of the child.

Materials and methods

Participants and procedures

Eligible for inclusion were all mothers and fathers of a child aged 0-18 years, diagnosed with MFS according to the revised Ghent criteria, [1] who visited the Amsterdam UMC expert center for children with Marfan syndrome and related disorders between June 2017 and May 2019. One week before the annual outpatient visit of their child, the parents were invited by letter to both complete the online DT-P and questions on sociodemographic characteristics on the KLIK website (www.hetklikt.nu). KLIK is an online Patient-Reported Outcome Measure (PROM portal) to systematically monitor different aspects of children with various chronic illnesses and their parents over time. Answers to the questionnaires (PROMs) were converted into a KLIK profile and discussed during the outpatient visit of their child. [25, 26]

The Medical Ethics Review Committee of the Amsterdam University Medical Centers, Amsterdam, the Netherlands, waived ethical approval under Dutch Law. Written informed consent was obtained from all parents for the reuse of data for research.

Measurements

Sociodemographic characteristics

Parents completed online questions on sociodemographic characteristics including their age, country of birth, educational level, employment status, marital status, number of children living at home, as well as the age, gender and educational level of their child with MFS.

Distress Thermometer for Parents (DT-P)

The DT-P is a validated screening instrument to identify overall distress, clinical distress and everyday problems in parents of a chronically ill child. [24, 37] The DT-P consists of 3 parts. First, parents rate their overall distress in the past week on a "thermometer" ranging from 0 (no distress) to 10 (extreme distress) with a thermometer score ≥ 4 indicating clinically relevant distress (further referred to as "clinical distress"). Second, the occurrence of everyday problems is inquired by 36 or 34 problem item yes/no questions (for parents of a child < 2 years or ≥ 2 years of age, respectively). There are six everyday problem domain scores: practical, social, emotional, physical, cognitive and parenting. These everyday problem domain scores are based on the number of times a "yes" is filled in for the everyday problem domain items. Third, additional questions inquire 1) perceived support from surroundings, 2) perceived lack of understanding from others concerning their situation, 3) parental chronic illness, 4) the wish to talk to a professional about their situation (yes, maybe or no). [24, 37] The internal consistency of the DT-P is acceptable with Cronbach's alphas ranging from 0.52 to 0.89. [24]

Marfan syndrome characteristics in children

The revised Ghent systemic score and the child-reported pain and fatigue were used to decribe the presence of MFS characteristics in children. Other characteristics that could have been used, for instance, aortic dilatation, lens luxation, foot-, lens-, pectus and/or scoliosis surgery, were too infrequently encountered. The revised Ghent systemic score is part of the revised Ghent criteria and is a method of assigning weighted values to the presence of clinical features that are associated with MFS. The score is calculated through the summation of applicable points (0-20). Experienced pain and fatigue of the child were discussed during the outpatient visit, one week after filling in the DT-P, and categorised in "no", "sometimes", or "often". Data were extracted from the child's medical file.

Statistical analysis

Mothers and fathers of a child with MFS were analysed as separate groups because of reported differences in distress levels. [14, 19-21, 23, 27] The Statistical Package for Social Sciences (SPSS) version 25.0 for Windows was used for all statistical analysis.

Descriptive analysis were used to describe the sociodemographic characteristics of the mothers, fathers without and with MFS and their children with MFS. Data were compared to those of 671 control-group mothers and 463 control-group fathers of a healthy child [24] using independent samples t-tests for numerical data and Chi-square tests for categorical data. Overall distress score, total everyday problem score and everyday problem domain scores were not distributed normally and so the median (interquartile range: IQR) was reported. Comparisons between groups were performed using Mann-Whitney U-tests: between (1) mothers of a child with MFS and control-group mothers; (2) mothers without MFS and mothers with MFS, both of a child with MFS; (3) mothers without MFS of a child with MFS, living together with an affected partner and control-group mothers; (4) fathers of a child with MFS and control-group fathers; (5) fathers without MFS and fathers with MFS, both of a child with MFS; (6) fathers without MFS of a child with MFS, living together with an affected partner and control-group fathers. Effect sizes (r) were calculated. The clinical distress score, everyday problem items and the additional questions were analysed with Chi-square/ Fisher's exact tests; odds ratios (OR) and confidence intervals (CI) were calculated. Following the previous DT-P studies, problem domain items were also analyzed for exploration and therefore, we did not correct for multiple testing. Correlation analysis (Spearman's rho) were used to explore associations between distress in parents and the presence of MFS characteristics of the child using the revised Ghent systemic score and the the child-reported pain and/or fatigue.

Table 1. Sociodemographic characteristics of parents of a child with MFS; control-group parents of a healthy child; children with MFS; and control-group healthy children

Parents	**Mothers**			**Fathers**		
	Mothers of a child with MFS (n=42)	**Control-group mothers of healthy children (n=671)**	**p value**	**Fathers of a child with MFS (n=25)**	**Control-group fathers of healthy children (n=463)**	***p value***
Age in years, mean (SD), range	40.4 (6.8), 25.7-51.9	38.8 (6.4), 18.1-63.3	.096	42.0 (7.2), 28.0-52.6	41.7 (7.4), 26.2-75.3	.835
Born in the Netherlands, n (%)	38 (90.5)	647 (96.6)	.068[a]	23 (92.0)	442 (95.5)	.332[a]
Educational level, n (%)[b]			.567			.095
Low	3 (7.3)	88 (13.1)		0	72 (15.6)	
Intermediate	17 (41.5)	300 (44.7)		10 (40.0)	193 (41.7)	
High	21 (51.2)	281 (41.9)		15 (60.0)	190 (41.0)[c]	
Paid employment, n (%)	32 (76.2)	545 (81.2)	.688	21 (84.0)	433 (93.5)[d]	.141
Marital status, n (%)			.991			.135
Married/living together	38 (90.5)	604 (90.0)		24 (96.0)	449 (97.0)	
Single/separated	4 (9.5)	64 (9.5)		1 (4.0)	13 (2.8)	
Widow	0	2 (0.3)		0	1 (0.2)	
Children living at home, n (%)			.876			.917
1	10 (23.8)	138 (20.6)		5 (20.0)	82 (17.7)	
2	23 (54.8)	378 (56.3)		15 (60.0)	274 (59.2)	
≥ 3	9 (21.4)	155 (23.1)		5 (20.0)	107 (23.1)	
Parental diagnosis of MFS, n (%)						
Yes	12 (28.6)	N/A		15 (60.0)	N/A	
No	27 (64.3)	N/A		10 (40.0)	N/A	
Not tested	3 (7.1)			0		

Children	**Children with MFS (n=43)**	**Control-group healthy children (n=1134)**	***p value***
Age in years, mean (SD), range	8.9 (4.7), 0.4-17.1	7.5 (5.4) 0.1-19.0	.109
Female gender (%)	19 (44.2)	551 (48.6)	.571
Educational level			.150
None (not yet started), n (%)	3 (7.0)	184 (16.2)	
regular day-care, n (%)	4 (9.3)	197 (17.4)	
regular primary school, n (%)	21 (48.8)	478 (42.2)	
special primary school, n (%)	1 (2.3)	5 (0.4)	
regular secondary school, n (%)	12 (27.9)	206 (18.2)	
special secondary school, n (%)	0 (0)	4 (0.4)	
post-secondary school, n (%)	2 (4.7)	60 (5.3)	
Having a parent with MFS, n (%)	31 (72.1)[$]	N/A	
Revised Ghent score, median (SD), range	6.7 (3.1), 1-13	N/A	
Child reported pain sometimes to often, n (%)	10 (23.3)	N/A	
Child reported fatigue sometimes to often, n (%)	19 (44.2)	N/A	

MFS, Marfan syndrome; p, probability; n, number; N/A, not applicable; High, higher vocational education, university; Intermediate: middle vocational education, higher secondary education, pre-university education; Low: primary education, lower vocational education, lower or middle general secondary education.

[a] Fishers Exact (<N = 5 in one cell).

[b] One missing.

[c] Eight missing.

[d] Two missing.

Results

Sociodemographic characteristics

In total, 42 mothers (29% with MFS) and 25 fathers (60% with MFS) of 43 children with MFS completed the DT-P (response rate 57%). Of the parents without MFS of a child with MFS, 14 mothers and 7 fathers lived together with an affected partner. No differences were found between the socio-demographic characteristics of mothers, fathers of a child with MFS and their children with MFS and control-group mothers, control-group fathers and their healthy children [see Table 1], and between mothers without MFS and mothers with MFS, both of a child with MFS, nor between fathers without MFS and fathers with MFS, both of a child with MFS (data not shown).

Marfan syndrome characteristics in the children

The diagnosis MFS was molecularly confirmed in 42 of the 43 children. The mean revised Ghent systemic score of the children was 6.7 (SD, 3.1; range, 1-13) [see Table 1]. "Sometimes to often" pain was reported in 23% and "sometimes to often" fatigue was reported in 44% of children with MFS [see Table 1].

Overall distress

Overall distress scores are shown in Table 2. The median overall distress score (IQR) of mothers of a child with MFS was significantly lower compared to control-group mothers (2, 1-4 vs. 3, 1-6; p = .049; r = -.07). Mothers without MFS reported significantly less overall distress compared to mothers with MFS, both of a child with MFS (1, 0-4 vs. 3.5, 2-5; p = .039; r = -.17). No significant differences in overall distress were found between the other groups.

Clinical distress

Clinical distress scores are shown in Table 2. No differences in percentages of clinical distress were found between mothers compared to control-group mothers (33% vs. 42%); mothers without MFS compared to mothers with MFS, both of a child with MFS (26% vs. 50%); mothers without MFS of a child with MFS, living together with an affected partner, compared to control-group mothers (29% vs. 42%); fathers of a child with MFS compared to control-group fathers (28% vs. 32%); fathers without MFS compared to fathers with MFS, both of a child with MFS (30% vs. 27%); fathers without MFS of a child with MFS, living together with an affected partner, compared to control-group fathers (29% vs. 32%).

Everyday problems

Total and everyday problem domain scores are shown in Table 3.

Table 2. DT-P overall and clinical distress score, problem domain scores and additional question scores of mothers and fathers of a child with MFS compared to control-group mothers and fathers of healthy children

Parents	Mothers					Fathers				
	Mothers of a child with MFS (n=42)	**Control-group mothers of healthy children (n=671)**	***p value***	**r / OR**	**z-score/ 95% CI**	**Fathers of a child with MFS (n=25)**	**Control-group fathers of healthy children (n=463)**	***p value***	**r /OR**	**z-score/ 95% CI**
Distress score										
Overall, median (IQR)	2 (1-4)	3 (1-6)	**.049**	-.07	z=-1,966	2 (1-6)	2 (1-5)	.68	-.02	z=-.418
Clinical %	33.3	42.3	.252	.68	.35-2.84	28.0	32.2	.662	.82	.33-2.0
Total problem domain score, median (IQR)[a]	3 (0-6)	4 (1-8)	**.032**	-.08	z=-2,148	1.5 (0-6)	2 (1-6)	.184	-.06	z=1,330
Problem domains										
Practical problems, median (IQR)	0.5 (0-2)	1 (0-2)	**.037**	-.08	z=-2,084	0 (0-1)	0 (0-1)	.880	-.01	z=-,151
Social problems, median (IQR)	0 (0-0)	0 (0-1)	**.032**	-.08	z=-2,142	0 (0-0)	0 (0-0)	.850	-.01	z=-,189
Emotional problems, median (IQR)	0 (0-2.25)	1 (0-3)	.257	-.04	z=-1,133	0 (0-1.5)	0 (0-2)	.372	-.04	z=-,892
Physical problems, median (IQR)	0.5 (0-2)	2 (0-3)	**.016**	-.09	z=-2,419	1 (0-2)	1 (0-2)	.839	-.01	z=-,203
Cognitive problems, median (IQR)	0 (0-0)	0 (0-1)	.102	-.06	z=-1,637	0 (0-0)	0 (0-0)	.655	-.02	z=-,447
Parenting problems child ≥2 years, median (IQR)[b]	0 (0-0)	0 (0-0)	.086	-.06	z=-1,718	0 (0-0)	0 (0-0)	.518	-.03	z=-,646
Parenting problems child <2 years[c]										
Additional questions support from others										
Experiencing enough support from others, and environment %	92.9	92.1	1.00[a]	1.11	.33-3.70	92.0	93.3	.683[d]	.82	.19-3.70

Table 2. Continued

Experiencing a lack of understanding from others, %	11.9	11.3	.909	1.05	.40-3.18	12.0	10.2	.733[d]	1.20	.35-4.17
Having a chronic illness themselves, %	40.5	20.3	**.002**	2.70	1.40-5.0	64.0	14.0	**< .0001**	11.11	4.55-25.0
Would like to talk to a professional about situation - Yes/Maybe, %	19.0	17.1	.751	1.14	.51-2.50	24.0	12.5	.098	2.22	.84-5.88

Significant differences at $p < .05$ are presented in bold; distress and domain scores: numerical data > not normal distributed > Mann–Whitney U tests with Z score (z) and effect size (r); binary data > Chi-square tests with odds ratio (OR) and confidence interval (CI).
Abbreviations: IQR, interquartile range; MFS, Marfan syndrome; p value, probability value; OR, odds ratio; r, effect size; n, number.
[a] Total problem score = the sum of item scores (yes = 1, no = 0) within 6 problem domains (practical, social, emotional, physical, cognitive and parenting).
[b] N = 41 MFS mothers, N = 560 reference mothers, N = 24 MFS fathers, N = 370 reference fathers.
[c] n = 1, no calculations possible.
[d] Fisher's Exact (<N = 5 in one cell).

Table 3. DT-P everyday problem-item scores of mothers and fathers of a child with MFS compared to control-group mothers and fathers of healthy children

Parents	**Mothers**					**Fathers**				
	Mothers of a child with MFS (n=42)	**Control-group mothers of healthy children (n=671)**	**OR**	**OR**	**95% CI**	**Fathers of a child with MFS (n=25)**	**Control-group fathers of healthy children (n=463)**	***p***	**OR**	**95% CI**
Practical problems										
Housing, %							3.7	.253[a]	2.27	.50-10
Work/study, %							25.9	.817	1.11	.45-2.70
Finances/insurance, %	0.0	16.7	**.001**[a]	[a]		12.0	14.5	1.00[a]	.80	.23-2.77
Housekeeping, %	11.9	21.6	.134	.49	.19-1.27	12.0	12.1	1.00[a]	.99	.29-3.44
Transport, %	4.8	4.6	1.00[a]	1.03	.24-4.55	4.0	3.9	1.00[a]	1.03	.13-8.33
Child care/child supervision, %	4.8	10.1	.419	.44	.10-1.89	4.0	5.4	1.00[a]	.73	.09-5.55
Leisure activities/relaxing, %	19.0	22.4	.617	.82	.37-1.79	20.0	14.9	.489	1.43	.52-4.00
Social problems										
Dealing with (ex)partner, %	2.4	12.4	**.049**[a]	.17	.02-.92	12.0	11.7	1.00[a]	1.03	.30-3.57
Dealing with family, %	4.8	10.9	.300[a]	.41	.10-1.72	4.0	6.7	1.00[a]	.58	.08-4.35
Dealing with friends, %	4.8	3.7	.669[a]	1.30	.30-5.56	12.0	1.5	**.011**[a]	9.09	2.12-33.33
Interacting with your child(ren), %	4.8	11.8	.213[a]	.37	.09-1.59	12.0	7.8	.440[a]	1.61	.46-5.56
Emotional problems										
Controlling emotions, %	19.0	27.4	.235	.62	.28-1.37	12.0	11.9	1.00[a]	1.01	.29-3.45
Self-confidence, %	9.5	22.7	.053[a]	.36	.13-1.02	12.0	12.7	1.00[a]	.93	.27-3.23
Fears, %	16.7	10.7	.156	1.67	.71-3.85	12.0	6.5	.234[a]	1.96	.56-7.14
Depression, %	21.4	31.9	.151	.58	.27-1.23	24.0	22.2	.838	1.10	.43-2.86
Feeling tense or nervous, %	38.1	36.1	.791	1.09	.57-2.08	24.0	26.3	.795	.88	.35-2.27
Loneliness, %	2.4	7.7	.356[a]	.29	.04-2.17	12.0	3.7	.076[a]	3.57	.97-12.50

Table 3. Continued

Feelings of guilt, %	9.5	17.4	.287[a]	.50	.17-1.43	12.0	7.3	.425[a]	1.72	.49-5.88
Use of substances (e.g. alcohol, drugs and/or medication), %	2.4	2.7	1.00[a]	.88	.12-6.66	0.0	3.0	1.00[a]	[b]	
Intrusive/recurrent thoughts about a specific event, %	21.4	20.4	.875	1.06	.50-2.27	16.0	13.8	.766[a]	1.19	.40-3.57
Physical problems										
Eating, %	4.8	12.4	.215[a]	.44	.08-1.49	16.0	4.8	**.037**[a]	3.85	1.20-12.50
Weight, %	19.0	26.2	.302	.66	.30-1.45	4.0	16.6	.155[a]	.21	.03-1.56
Sleep, %	26.2	29.7	.633	.84	.41-1.69	12.0	21.4	.322[a]	.50	.15-1.69
Fatigue, %	35.7	55.7	**.011**	.44	.23-.84	40.0	44.1	.690	.85	.37-1.92
Out of shape/condition, %	11.9	20.9	.162	.51	.20-1.33	24.0	19.0	.537	1.35	.52-3.45
Pain, %	19.0	24.3	.440	.74	.33-1.61	16.0	18.1	1.00[a]	.86	.29-2.56
Sexuality, %	2.4	10.6	.111[a]	.21	.03-1.52	16.0	8.9	.274[a]	1.96	.64-5.88
Cognitive problems										
Concentration, %	7.1	17.9	.091[a]	.35	.12-1.16	20.0	11.2	.184	1.96	.71-5.56
Memory, %	14.3	22.4	.220	.58	.24-1.41	20.0	13.6	.369	1.59	.57-4.35
Parenting problems ≥2										
Dealing with your child, %	4.9	10.9	.297[a]	.42	.10-1.79	4.2	9.7	.714[a]	.40	.05-3.03
Dealing with the feelings of your child, %	7.3	9.3	1.00[a]	.77	.23-2.56	0.0	8.6	.242[a]	[b]	
Talking about the disease/ consequences with your child, %	0.0	3.0	.621[a]	[b]		0.0	2.7	1.00[a]	[b]	

Table 3. Continued

Independence of your child, %	2.4	7.5	.348[a]	.31	.04-2.27	8.3	7.6	.703[a]	1.11	.25-5.00
Following advice about treatment/giving medication, %	0.0	3.4	.633[a]	[b]		4.2	3.0	.535[a]	1.41	.18-11.11

Significant differences at $p < .05$ are presented in bold.
Item scores: Chi2 tests with OR and 95% CI
[a] Fisher's Exact (<N=5 in one cell)
[b] no calculation possible due to n=0 in one cell

Mothers of a child with MFS reported a significantly lower median (IQR) total everyday problem domain score compared to control-group mothers (3, 0-6 vs. 4, 1-8; p = .03; r = -.08), with significantly lower scores for the practical problem domain (0.5, 0-2 vs. 1, 0-2; p = .037; r = -.08); social problem domain (0, 0-0, vs. 0, 0-1; p = .032; r = -.08) and physical problem domain (0.5, 0-2 vs. 2, 0-3: p =.016, r = -.09). No significant differences in total and everyday problem domain scores were found between the other groups.

Everyday problem items

Everyday problem items are shown in Table 3.

When looking at the everyday problem items within the 6 problem domains, mothers of a child with MFS reported significantly less often everyday problems on the items finances (0% vs. 16.7%, p = .001, n = 0 in a cell, no OR calculation possible); dealing with (ex) partner (2.4% vs. 12.4%, p = .049, OR = .17, 95% CI .02 - .92) and fatigue (35.7% vs. 55.7%, p = .01, OR = .44, 95% CI .23 - .84), compared to control-group mothers. Mothers without MFS of a child with MFS, living together with an affected partner, reported significantly more often everyday problems on the item fears compared to control-mothers (28.6% vs. 10.7% , p = .035, OR = 3.3, 95% CI 1.02 - 10.89). Fathers of a child with MFS reported significantly more often everyday problems on the items dealing with friends (12% vs. 1.5%, p = .01, OR = 9.09, 95% CI 2.12 - 33.33) and eating (16% vs. 4.8%, p = .037, OR = 3.85, 95% CI 1.20 - 12.50), compared to control-group fathers. Fathers without MFS of a child with MFS, living together with an affected partner, reported significantly more often everyday problems on the items dealing with friends (14.3% vs. 1.5%, p = .02, OR = 8.7, 95% CI .95 - 80.30) and interacting with your child(ren) (28.6% vs. 7.7%, p = .043, OR = 4.8, 95% CI .95 - 25.60) compared to control-group fathers. No significant differences in the everyday problem items were found between the other groups.

Support from others

Mothers and fathers without and with MFS of a child with MFS, living together with a healthy or an affected partner did not differ significantly from control-group parents with respect to experiencing to receive enough support from surroundings, experiencing a lack of understanding from others and the wish to talk with a professional about their situation [see Table 3]. Both mothers and fathers of a child with MFS indicated more often to have a chronic illness than parents of a healthy child (40% vs. 20%, p = .002, OR = 2.7, 95% CI 1.40 - 5.0; 64% vs. 14%, p = <.0001, OR = 11.11, 95% CI 4.55 - 25.0) [see Table 3].

Associations of distress and Marfan syndrome characteristics of children

There were no significant associations between distress on the one side, and the revised Ghent systemic score of the child, the child-reported pain and/or fatigue on the other side.

Discussion

This study is the first quantitative study reporting on distress and everyday problems in mothers and fathers without and with MFS parenting a child with MFS. Surprisingly, parents of a child with MFS did not show more signs of clinical distress than parents of healthy children. The total group of mothers of a child with MFS even reported significantly lower overall distress and everyday problems compared to control-group mothers, albeit with small effect sizes.

This was an unexpected finding given the well-known risk of (acute) medical MFS related complications, [1, 2, 6-10] the need for regular medical follow up [3-5] for both children and also for the parent with MFS, and the perceived significant impact of MFS on daily (physical) functioning of children, parents and the family. [9-11, 30-36, 38] Parents of children with a variety of other chronic diseases have been shown to often suffer from anxiety and depression, [14] parenting stress [15] and parental burden. [16-18] In previous studies in which parental distress was measured by the DT-P compared to control-group parents, high overall distress and everyday problems were found in parents of children with cancer, [19] mucopolysaccharidosis type III, [21] and in children needing home parenteral nutrition. [20] In parents of children with Inflammatory Bowel Disease, [22] a worsening disease course was directly associated with increased distress. In MFS, however, the clinical features evolve during life, and high-risk complications or surgery, are only infrequently encountered during childhood. The low level of medical emergencies requiring hospital visits or hospitalisation in MFS in childhood may partially explain why we did not find elevated distress nor any association between distress and the childs' revised Ghent systemic score, child-reported pain and/or fatigue. However, medical professionals should be aware that whenever acute medical complications arise e.g. lens luxation, pneumothorax, aortic rupture, musculoskeletal surgery or other surgery in a child or a parent with MFS, distress levels in parents might become clinically relevant and should be addressed accordingly.

Another hypothesis for the unexpected results of our study might be that the parents had developed strong coping strategies. The term "coping" is defined as "the thoughts and behaviours used to manage the internal and external demands of situations that are appraised as stressful, so that it is possible to live and deal with stressful situations and reduce internal and external conflicts and demands". [39] This is endorsed by a review reporting on psychosocial factors in adults with MFS; despite the psychologically distressing aspects of the diagnosis MFS, most patients were able to manage their stressors and exhibited a higher than average life satisfaction because of efficient coping and reliance on self-efficacy. [36] In our recent qualitative paper, adolescents with MFS also described positive coping strategies as seeking social support, having a humorous

and relaxed outlook on life, reappraising their disease and disability in a positive light, pursuing a healthy lifestyle, and trying to plan their activities well to handle the impact of MFS on their physical and psychosocial functioning. [38] These adolescents may have copied these strong coping strategies from their parents or the parents may have adopted these strategies from their child.

Little is known about the impact on distress and everyday problems in parents, of parenting a child with a connective tissue disorder (MFS, Ehlers-Danlos syndromes, Loeys Dietz syndrome) and being affected by the same disorder or caring for an affected partner and an affected child. In our study, although not significantly different, mothers with MFS tended to report higher clinical distress (50%) compared to control-group mothers (42%). It is known that in adults, MFS negatively affects family life, physical activities, psychosocial development, education, work, and reproductive planning. [9, 10, 33-36] Furthermore having a chronic illness as a parent adversely affects parental health-related quality of life. [13, 28] In our study, healthy parents of a child with MFS, living together with an affected partner, did not show more signs of clinical distress compared to control-group parents of healthy children. However, these mothers reported significantly more often everyday problems on the item fears and fathers reported more often everyday problems on the items dealing with friends and interacting with your child(ren). Because of the negative impact of MFS in adults, e.g. personal and family life, medical professionals should be extra alert for distress in parents of families with both a child and a parent with MFS.

Our study has some limitations. First, the sample size might have been too small to find more subtle differences between the groups. Second, all parents were recruited from the Amsterdam UMC expert center for children with Marfan syndrome and related disorders. Third, not for every child both parents filled in the questionnaire. One may argue that the one parent with the least problems of the two was more likely to fill in the questionnaire. Also, the DT-P is linked to the childs' hospital visit and asks questions concerning distress in the past week. Parents with MFS with medical complications themselves, busy family schedules, other problems or elevated distress might have cancelled the appointment. Therefore, the data may underestimate the distress and everyday problems.

In conclusion, parents of a child with MFS did not show more clinical signs of distress compared to parents of healthy children. Mothers of a child with MFS even reported less overall distress and total everyday problems screened by the DT-P. The distress in parents was not associated with the children's revised Ghent systemic score, child-reported pain and/or fatigue. However, clinical distress was reported in approximately one-third of parents and may further increase in case of acute medical complications in the child or parent with MFS. We, therefore, advise monitoring distress in parents of a child with MFS so that targeted support can be provided whenever indicated.

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CHAPTER 5

"Me, my friends and family skiing together" by Feline Tijhuis (16 years)

Heritable Connective Tissue Disorders in childhood: Fatigue, pain disability and general health

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Abstract

Background Heritable Connective Tissue Disorders (HCTD) show an overlap in the physical features that can evolve in childhood. It is unclear to what extent children with HCTD experience burden of disease. This study aims to quantify fatigue, pain, disability and general health with standardized validated questionnaires.

Methods This observational, multicenter study included 107 children, aged 4–18 years, with Marfan syndrome (MFS), 58%; Loeys-Dietz syndrome (LDS), 7%; Ehlers-Danlos syndromes (EDS), 8%; and hypermobile Ehlers-Danlos syndrome (hEDS), 27%. The assessments included PROMIS Fatigue Parent Proxy and Pediatric self-report, pain and general health Visual-Analogue-Scales (VAS) and a Childhood Health Assessment Questionnaire (CHAQ).

Results Compared to normative data, the total HCTD-group showed significantly higher parent-rated fatigue T-scores (M = 53 (SD = 12), p = 0.004, d = 0.3), pain VAS scores (M = 2.8 (SD = 3.1), p < 0.001, d = 1.27), general health VAS scores (M = 2.5 (SD = 1.8), p < 0.001, d = 2.04) and CHAQ disability index scores (M = 0.9 (SD = 0.7), p < 0.001, d = 1.23). HCTD-subgroups showed similar results. The most adverse sequels were reported in children with hEDS, whereas the least were reported in those with MFS. Disability showed significant relationships with fatigue (p < 0.001, r_s = 0.68), pain (p<.001, r_s = 0.64) and general health (p< 0.001, r_s = 0.59).

Conclusions Compared to normative data, children and adolescents with HCTD reported increased fatigue, pain, disability and decreased general health, with most differences translating into very large-sized effects. This new knowledge calls for systematic monitoring with standardized validated questionnaires, physical assessments and tailored interventions in clinical care.

Introduction

Heritable Connective Tissue Disorders (HCTD) are characterized by pathological connective tissue fragility in multiple organ systems. The diagnosis is based on clinical criteria and/or molecular confirmation by a causative genetic variant. [1-3] The phenotypes of the most common HCTD, Marfan syndrome (MFS), [1] Loeys-Dietz syndrome (LDS) [2] and Ehlers-Danlos syndromes, [3] show an overlap in the musculoskeletal, cardiovascular and cutaneous features [1-7] that can evolve in childhood. It is unclear to what extent children and adolescents with HCTD experience physical impairments, limitations in activities and burden of disease, and whether there is a difference among HCTD-subgroups. [8]

In previous qualitative semi-structured interview studies, parents of children with MFS (4–12 years) and adolescents with MFS (12–18 years) experienced problems of physical functioning, participation in activities and daily life and keeping up with peers. [9, 10] Furthermore, studies in children with MFS and hEDS have reported fatigue and pain to negatively impact daily (physical) functioning, [7, 11-19] a high incidence of pain-related disability [17] and deteriorating physical functioning over time. [20] To our best knowledge, no quantitative studies, using validated questionnaires, have been conducted into pain, fatigue and disability in children with MFS, LDS and molecularly confirmed types of EDS (hereafter EDS). A few studies in children and adolescents with hEDS and Hypermobility Spectrum Disorders (HSD, the current label for patients with joint hypermobility and musculoskeletal complications who do not fulfil the criteria for hEDS) [7] reported on increased fatigue and pain, [18] generalized hyperalgesia, [21] and improvement of disability after following an outpatient multidisciplinary rehabilitation treatment program. [17] Regarding adults with HCTD, it has been reported that patients with MFS, LDS, EDS and hEDS have persistent fatigue, pain, disability and burden of disease. [4-6, 14, 16, 22-28]

This study aims to gain better insight into the prevalence and severity of fatigue, pain, disability and general health in children and adolescents diagnosed with the most common HCTD using standardized validated questionnaires.

Methods

Study Design

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

Participants

Those eligible for inclusion were all children and adolescents, aged 4–18 years, with MFS, [1] LDS, [2] EDS, [3] hEDS, [3] and HSD. [7]

Procedures

The expert centers 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, included participants in the study. Additionally, the MFS and EDS patient associations in the Netherlands announced the study information on their websites. Participants could contact the research team by email or phone. Children and parents were invited by letter and written informed consent was obtained. The study took place from February 2019 to March 2020. The survey completion time was 80–95 min. 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.

Participant Characteristics

A custom-made parent questionnaire collected information on the sex, age, nationality and HCTD diagnosis of their child and on their own sex, age and nationality. One of the parents completed the questionnaire.

PROMIS Fatigue Pediatric Self-Report and Parent Proxy

The Patient Reported Outcomes Measurement Information System's (PROMIS) Fatigue 10a Pediatric v2.0 short form and Fatigue 10a Parent Proxy v2.0 short form assess self-reported fatigue in children aged 8-18 years, and parent-reported fatigue in children under eight, respectively. Both questionnaires contain 10 fatigue statements that pertain to the degree of fatigue and the impact of fatigue on physical, mental and social activities, as experienced during the last seven days. Each question has five response options (never = 1, rarely = 2, sometimes = 3, often = 4, always = 5). To calculate the total raw score, the values of the response to each question are summed and then rescaled into a standardized T-score with a mean of 50 and a standard deviation (SD) of 10. Both questionnaires are widely used rating scales with well-studied and excellent psychometric properties, and they discriminate well between disease severities. [29-31]

Childhood Health Assessment Questionnaire (CHAQ), Pain VAS and General Health VAS

The Dutch version of the CHAQ [32] assesses functional ability in daily life activities and distinguishes between the following eight domains: dressing, arising, eating, walking, hygiene, reach, grip and activities (30 items). The response scores for each item range from 0–3. The highest score of an item within a domain determines the domain score. The utilization of assistance or aids in a domain sets the domain score to a minimum of two. The mean score of the eight domains determines the CHAQ disability index (CHAQ-DI) and ranges from zero (no disability) to three (disabled). [32-33] Children under eight are proxy reported. Children aged 8–18 years self-report. The pain and general health Visual Analogue Scales (VASs) supplement the CHAQ. The pain VAS assesses subjective pain over the last week. The intensity of pain is scored on a 0–100 scale, with zero referring to "no pain" and 100 to "very severe pain". Children under eight are proxy reported. Children aged 8-18 years self-report. The general health VAS assesses current subjective general health. General health is scored on a 0–100 scale, with zero referring to "very good general health" and 100 to "very poor general health". Children aged 4-18 years are proxy reported. The CHAQ, pain VAS and general health VAS are widely used rating scales with well-studied and excellent psychometric properties, and they discriminate well between children with chronic conditions and healthy children. [32-35]

Statistical analysis

Online survey data were exported from the Castor database to the Statistical Package for Social Science (SPSS) version 26.0. Data were analyzed as the total HCTD-group and separately, as the HCTD-subgroups: MFS, LDS, EDS and hEDS. The group sizes of the HCTD-subgroups EDS (n = 9) and LDS (n = 7) were small, and the analysis were for explorative interpretation only. Data were checked for errors, missings and outliers. Sex, age and nationality of the HCTD-group, HCTD-subgroups and of the parent, who completed the survey, were analyzed using descriptive analysis. To compare the normative categorical data, age groups, sex and nationality, of the PROMIS Fatigue, CHAQ, pain VAS and general health VAS [32-33] to the HCTD-group and HCTD-subgroups data, chi–square tests were used and presented as Odds Ratios (OR) and 95% confidence intervals (CI). [36] The normality of the distributions was visually inspected using normality plots and tested using Shapiro–Wilk tests. The CHAQ-DI scores, pain VAS scores and general health VAS scores of the HCTD-group and HCTD-subgroups were not all distributed normally; these data were reported using the median and interquartile range (IQR). However, normative data of these questionnaires have been reported using means and standard deviation (SD). Consequently, for comparison reasons, our data were also reported by means (SD). To compare the normative scores of the PROMIS Fatigue, CHAQ-DI, pain VAS and general health VAS [31, 33] to the HCTD-group's and HCTD-subgroup's scores, independent-sample t-tests were used. Among the HCTD-subgroups, Kruskal–Wallis tests and Mann–Whitney U tests were used. Severe fatigue was defined as a standardized T-score > 70, based on the PROMIS Fatigue normative T-scores. [31, 36, 37] Severe disability was defined as a standardized z-score of < -2, based on the normative CHAQ-DI scores. [32, 33, 36] To compare the severe fatigue and severe disability percentages of the normative scores to the HCTD-group and HCTD-subgroups, chi–square tests were used. The effect sizes were calculated. For parametric tests, Cohen's d was defined as the difference between the mean and the normative data mean, divided by the pooled standard deviations, with values of 0.2, 0.5 and 0.8 defined as the thresholds for small, moderate and large effects, respectively. [36] For non-parametric tests, Mann–Whitney U test's r was defined as the

z-score divided by the square root of observations, with values of 0.1, 0.3 and 0.5 defined as the thresholds for small, moderate and large effects, respectively. Spearman's rho r_s, a non-parametric test, was used to explore relationships between fatigue, pain, disability and general health in the HCTD-group and the HCTD-subgroups, where the value r_s = 1 means a perfect positive correlation and the value r_s = -1 means a perfect negative correlation. [36] A p-value ≤ 0.05 was considered statistically significant. [36]

Results

Participants

Table 1 shows the sex, age and nationality of children of the HCTD-group; the HCTD-subgroups: MFS, LDS, EDS and hEDS; and of the parents who completed the survey. Initially, 156 children and adolescents agreed to participate, of whom five were not diagnosed with HCTD. They were excluded. Another 44 participants did not complete the survey and, consequently, there are no data related to these participants. In total, 107 children and adolescents with HCTD participated: MFS, 58%; LDS, 7%; EDS, 8%; hEDS, 27%; and HSD, 0%. The mean age (SD) was 10.0 (4.1) years and 55% of the children were male.

Fatigue Pediatric self-report

Table 2 and Figure 1 show the PROMIS Fatigue 10a Pediatric v2.0 short form and the PROMIS Fatigue 10a Parent Proxy v2.0 short form T-scores of the normative data, the HCTD-group and the HCTD-subgroups, MFS, LDS, EDS and hEDS; comparisons between the normative T-scores and the HCTD-group's T-scores; and comparisons among the HCTD-subgroup's T-scores.

Compared to normative T-scores, the HCTD-group did not differ significantly, indicating no increased fatigue; the HCTD-subgroup hEDS reported significantly higher T-scores, translating into a large-sized effect, indicating increased fatigue ($p < 0.001$, $d = 1.1$); and the HCTD-subgroup MFS reported significantly lower T-scores, translating into a large-sized effect, indicating decreased fatigue ($p < 0.001$, $d = 0.6$).

Compared to normative data, the percentage of children with a T-score above the severe fatigue cut-off was significantly greater in the HCTD-subgroups EDS and hEDS (OR 6.6, 95% CI 2.5 – 19.6, p = 0.03; OR 6.6, 95% CI 1.2 – 36.5, p < 0.001, respectively).

Table 1. Participants: sex, age and nationality of children of the HCTD-group, the HCTD-subgroups: MFS, LDS, EDS, hEDS; and of the parents who completed the survey.

Child	**HCTD**	**MFS**	**LDS**	**EDS**	***hEDS***	**Among HCTD- subgroups p-Value**
n (%)	107 (100)	62 (58)	7 (7)	9 (8)	29 (27)	
Sex, n (%), Female	48 (45)	20 (32)	5 (71)	6 (67)	17 (59)	0.02*
Age in years, M (SD)	10.2 (4.0)	10.1 (4.1)	11.0 (3.9)	10.8 (4.8)	10.0 (3.7)	0.90
Nationality, n (%)						0.03*
Dutch	97 (90)	56 (90)	6 (86)	6 (67)	29 (100)	
Belgium	10 (10)	6 (10)	1 (14)	3 (33)	0 (0)	
Parent						
n (%)	107 (100)	62 (58)	7 (7)	9 (8)	29 (27)	
Sex, n (%), Female	86 (80)	46 (74)	6 (86)	7 (78)	27 (93)	0.20
Age in years, M (SD)[a]	42,5 (7.1)	43.5 (8.1)	42.3 (6.3)	42.6 (4.2)	40.2 (4.9)	0.18
Nationality, n (%)						0.03*
Dutch	97 (90)	56 (90)	6 (86)	6 (67)	29 (100)	
Belgium	10 (10)	6 (10)	1 (14)	3 (33)	0 (0)	

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; a missing 2; * significant difference.

Explorative analysis of fatigue among the HCTD-subgroups showed significantly higher fatigue scores for in the hEDS-subgroup compared to the MFS-subgroup and LDS-subgroup, translating into large-sized effects ($p < 0.001$, $r = 0.61$; $p = 0.006$, $r = 0.61$, respectively).

Table 2. The Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue 10a – Pediatric v2.0 Short form and the PROMIS Fatigue 10a – Parent Proxy v2.0 Short form: T-scores of normative data, the HCTD-group and the HCTD-subgroups: MFS, LDS, EDS and hEDS; comparisons between normative T-scores and HCTD-group T-scores; and comparisons among HCTD-subgroup T-scores.

PROMIS Fatigue Pediatric self-report 8–18 years	HCTD	norm	HCTD vs norm p-value	Effect size Cohen's d/ OR(95%CI)	MFS	LDS	EDS	hEDS	Among HCTD-subgroups p-value
n (%)	62 (100)[a]	3042 (100)			36 (58)[b]	5 (8)	6 (10)[c]	15 (24)[c]	
Sex, n (%), Female	30 (48)	1578 (52)	.6		14 (39)	4 (80)	4 (67)	8 (53)	0.24
Age-groups, n (%)			0.08*						0.50
8-12 years	26 (42)	1616 (53)							
13-18 years	36 (58)	1426 (47)							
T scores, M (SD)	49 (13)	50 (10)	0.44		44 (11)	47 (8)	52 (19)	61 (9)	<0.001*
T score > 70, n (%)	8 (13)	213 (7)	0.07*	2.0 (0.94-4.1)	1 (3)	0	2 (33)	5 (33)	0.02*
PROMIS Fatigue Parent proxy 4–18 years									
n (%)	98 (100)[a]	1980			57 (58)[b]	7	9	25 (26)[c]	
T scores, M (SD)	53 (12)	50 (10)	0.004*	0.27	48 (11)	50 (9)	56 (13)	63 (8)	<0.001*
T score > 70, n (%)	17 (16)	138 (7)	<0.001*	2.83 (1.63 - 4.9)	3 (5)	0 (0)	3 (33)	11 (38)	0.023*

CI, Confidence Interval; EDS, Ehlers-Danlos Syndromes; HCTD, Heritable Connective Tissue Disorders; hEDS, hypermobile Ehlers-Danlos syndrome; LDS, Loeys-Dietz Syndrome; MFS, Marfan syndrome; n, number; OR, Odds Ratio; p, probability; PROMIS, Patient Reported Outcomes Measurement Information System; SD, standard deviation; a missing 9; b missing 5; c missing 2; * significant difference.

Fatigue Parent Proxy

Compared to normative T-scores, the HCTD-group reported significantly higher T-scores, translating into a small to medium-sized effect ($p = 0.004$, $d = 0.3$); and the HCTD-subgroup hEDS also reported significantly higher T-scores, translating into a very large-sized effect ($p < 0.001$, $d = 1.4$). Both results indicate increased fatigue. The other HCTD-subgroups showed no significant differences.

Compared to normative data, the percentage of children with a T-score above the severe fatigue cut-off was significantly greater for the HCTD-group and HCTD-subgroups EDS and hEDS (OR 2.8, 95% CI 1.6 – 4.9, $p < 0.001$; OR 6.7, 95% CI 1.7 – 27.0, $p < 0.001$; OR 10.5, 95% CI 4.7 – 23.5, $p < 0.001$, respectively).

Explorative analysis of fatigue among the HCTD-subgroups showed significantly higher fatigue scores for the hEDS-subgroup compared to the MFS-subgroup and LDS-subgroup, translating into large-sized effects ($p < 0.001$, $r = 0.57$; $p < 0.001$, $r = 0.51$, respectively).

Disability

Table 3 and Figure 1 show the Childhood Health Assessment Questionnaire (CHAQ), pain VAS and general health VAS: CHAQ domain scores, CHAQ disability index scores, pain VAS scores and general health VAS scores of the normative data, the HCTD-group and the HCTD-subgroups: MFS, LDS, EDS and hEDS; comparisons between the normative scores and the HCTD-group's scores; and comparisons among the HCTD-subgroup scores.

Compared to normative CHAQ-DI scores, the HCTD-group and all of the HCTD-subgroups reported significantly higher scores, translating into medium to very large-sized effects, [32] indicating increased disability (HCTD ($p < 0.001$, $d = 1.23$), MFS ($p < 0.001$, $d = 0.78$), LDS ($p = 0.003$, $d = 1.10$), EDS ($p < 0.001$, $d = 1.11$), hEDS ($p < 0.001$, $d = 2.28$)).

Compared to normative data, the percentage of children with a score above the severe disability cut-off was significantly greater for the HCTD-group and all of the HCTD-subgroups (HCTD (OR 24.3, 95% CI 5.6 – 104.7, $p < 0.001$), MFS (OR 11.3, 95% CI 2.4 – 52.2, $p < 0.001$), LDS (OR 15.6, 95% CI 1.8 – 135.1, $p = 0.001$), EDS (OR 31.2, 95% CI 4.6 – 213.5, $p < 0.001$), hEDS (OR 123.5, 95% CI 23.1 – 660.7, $p < 0.001$), respectively).

Children with HCTD with severe disability (z-score ≤ -2) did not differ significantly with respect to age ($p = 0.43$) or sex ($p = 0.58$) compared to children without disability (z-score ≥ 0). Explorative analysis of disability (CHAQ-DI) among the HCTD-subgroups showed significantly higher disability scores, translating into medium to large-sized effects in the hEDS-subgroup compared to MFS-subgroup, LDS-subgroup and EDS-subgroup ($p < 0.001$, $r = 0.58$; $p = 0.005$, $r = 0.46$; $p = 0.043$, $r = 0.32$, respectively).

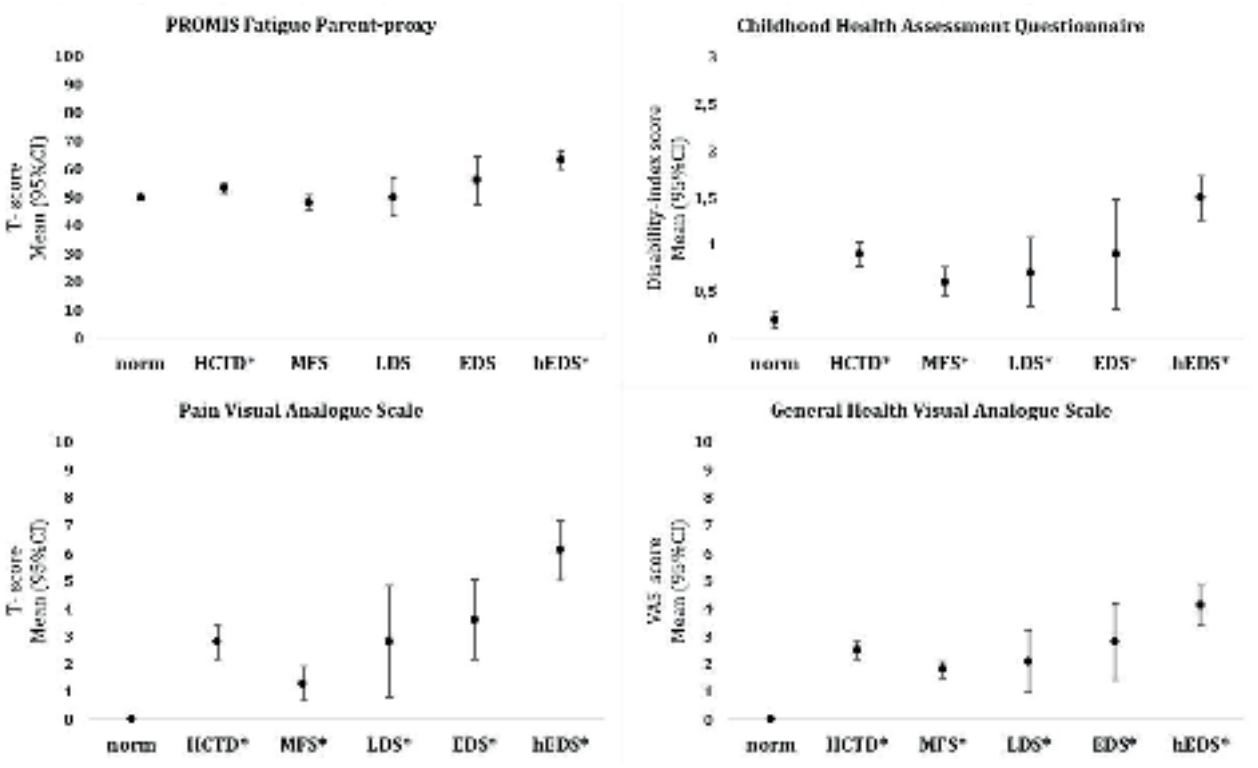

Figure 1. This figure shows the mean 95% confidence interval (CI) of the Childhood Health Assessment Questionnaire disability index (CHAQ-DI) score (range 0–3), PROMIS Fatigue Parent Proxy T-score (range 0–100), pain Visual Analogue Scale (VAS) score (range 0–10) and general health VAS score (range 0–10) of the normative data, the Heritable Connective Tissue Disorders (HCTD) group, and the following HCTD-subgroups: Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), Ehlers-Danlos Syndromes (EDS) and hypermobile Ehlers-Danlos syndrome (hEDS). * Compared to the normative data, this HCTD (sub)-group shows a significant difference.

Table 3. Childhood Health Assessment Questionnaire (CHAQ), pain VAS and general health VAS: CHAQ domain scores, CHAQ disability-index scores, pain VAS scores and general health VAS scores; of normative data, the HCTD-group and the HCTD-subgroups: MFS, LDS, EDS and hEDS; comparisons between normative scores and HCTD-group scores; and among HCTD-subgroup scores.

CHAQ	HCTD	norm	HCTD vs norm p-value	Effect size Cohen's *d*	MFS	LDS	EDS	hEDS	Among HCTD-subgroups p-value
n (%)	99 (100)[a]	80			58 (59)[b]	7 (7)	9 (9)	25 (25)[b]	
Sex, n (%) Female	44 (45)	33 (41)	.59		19 (33)	5 (71)	6 (67)	14 (56)	0.04
Age in years, M (SD)	10.1 (4.1)	8.1 (3.6)	<0.001*	0.49	10.1 (4.2)	11.0 (3.9)	10.8 (4.8)	9.6 (3.7)	0.81
Domain scores (0–3) M (SD)									
Dressing	.8 (1.0)	.5 (.8)	0.03*	0.33	0.6 (.9)	.4 (0.8)	1.0 (0.9)	1.3 (1.3)	
Arising	.7 (.8)	.1 (.3)	<0.001*	0.99	0.4 (.7)	.9 (0.9)	0.7 (0.8)	1.4 (0.9)	
Eating	1.0 (.9)	.4 (.7)	<0.001*	0.74	0.7 (.8)	.7 (0.8)	0.9 (0.9)	1.7 (0.9)	
Walking	.6 (.9)	.0 (.1)	<0.001*	0.94	0.3 (.7)	.1 (0.4)	0.6 (0.9)	1.3 (0.9)	
Hygiene	.8 (1.0)	.3 (.6)	<0.001*	0.60	0.5 (.8)	.1 (0.4)	0.8 (0.9)	1.4 (1.1)	
Reach	.9 (.8)	.2 (.5)	<0.001*	1.0	0.5 (.8)	.9 (0.7)	0.9 (0.9)	1.5 (0.6)	
Grip	1.1 (.9)	.2 (.6)	<0.001*	1.18	0.8 (.8)	1.1 (0.9)	1.1 (1.1)	1.7 (0.9)	
Activity	1.1 (1.0)	.2 (.5)	<0.001*	1.14	0.7 (.8)	1.1 (0.7)	1.4 (1.2)	1.9 (0.7)	
CHAQ-DI scores (0–3)									
M (SD); median (IQR)	0.9 (0.7); 0.6 (1.1)	0.2 (0.4)	<0.001*	1.23	0.6 (0.6); 0.4 (0.8)	0.7 (0.5); 0.6 (0.6)	0.9 (0.9); 0.5 (1.8)	1.5 (0.6); 1.5 (1.1)	< 0.001*
Pain VAS scores (0-10)									
n (%)	93 (100)[c]	80			54 (58)[a]	7 (7)	9 (10)	23 (25)[d]	
M (SD); median (IQR)	2.8 (3.1); 1.9 (5.5)	0.0 (0.2)	<0.001*	1.27	1.3 (2.3); 0 (2.0)	2.8 (2.7); 2.5 (5.7)	3.6 (2.2); 2.9 (3.2)	6.1(2.7); 7.0 (3.7)	< 0.001*
General health VAS scores (0-10)									
n (%)	82 (100)[e]	80			48 (59)[f]	6 (7)[g]	6 (7)[h]	22 (27)[i]	
M (SD); median (IQR)	2.5 (1.8); 2.0 (2.5)	0.0 (0.1)	< 0.001*	2.04	1.8 (1.2); 1.5 (1.6)	2.1 (1.5); 2.4 (2.5)	2.8 (2.1); 2.3 (1.7)	4.1(1.8); 4.1 (3.3)	< 0.001*

CHAQ, Childhood Health Assessment Questionnaire; CI, Confidence Interval; *d*, Cohen's d effect size; EDS, Ehlers-Danlos Syndromes; HCTD, Heritable Connective Tissue Disorders; hEDS, hypermobile Ehlers-Danlos syndrome; IQR, interquartile range; LDS, Loeys-Dietz Syndrome; MFS, Marfan syndrome; n, number; p, probability; SD, standard deviation; VAS, Visual Analog Scale; [a] missing 4; [b] missing 8; [c] missing 8; [d] missing 6; [e] missing 14; [f] missing 14; [g] missing 1; [h] missing 3; [i] missing 7; [j] missing 15

The assistance of another person was required in 41% in the HCTD-group participants (MFS, 27%; LDS, 28%; EDS, 33 %; and hEDS, 76%), mainly for errands and chores. The utilization of aids or devices during activities was needed in 46% (MFS, 29%; LDS, 57%; EDS, 56%; and hEDS, 80%). Special utensils and a wheelchair were used the most.

Pain

Compared to normative pain VAS scores, the HCTD-group and all of the HCTD-subgroups reported significantly higher scores, translating into medium to very large-sized effects, [33] indicating a higher pain intensity during the last week (HCTD ($p < 0.001$, $d = 1.27$), MFS ($p < 0.001$, $d = 0.80$), LDS ($p < 0.001$, $d = 1.46$), EDS ($p < 0.001$, $d = 2.30$), hEDS ($p < 0.001$, $d = 3.17$)).

Explorative analysis of the pain VAS scores among the HCTD-subgroups showed a significantly higher pain intensity translating to medium to large-sized effects for the hEDS-subgroup compared to the MFS-subgroup, LDS-subgroup and EDS-subgroup ($p < 0.001$, $r = 0.63$; $p = 0.016$, $r = 0.54$; $p = 0.021$, $r = 0.40$, respectively). The group of children with HCTD with a reported pain VAS score ($n = 93$) compared to the group of children without a reported pain VAS score (missings = 14), did not differ significantly with respect to age ($p = 0.98$) or sex ($p = 0.46$).

General Health

Compared to normative General health VAS scores, the HCTD-group and all of the HCTD-subgroups reported significantly higher scores, translating into very large-sized effects indicating decreased general health (HCTD ($p < 0.001$, $d = 2.04$), MFS ($p < 0.001$, $d = 2.1$), LDS ($p < 0.001$, $d = 2.0$), EDS ($p < 0.001$, $d = 1.9$) and hEDS ($p < 0.001$, $d = 3.3$)).

Explorative analysis of general health VAS scores among the HCTD-subgroups showed significantly decreased general health, translating into medium to large-sized effects, for the hEDS-subgroup compared to the MFS-subgroup and LDS-subgroup ($p < 0.001$, $r = 0.58$; $p = 0.025$, $r = 0.42$, respectively). The group of children with HCTD with a reported general health VAS score ($n = 82$) compared to the group of children without a reported general health VAS score (missings = 25), were not significantly different with respect to age ($p = 0.140$) or sex ($p = 0.72$).

Correlations

Disability in the HCTD-group was significantly positively correlated to fatigue, in both parent proxy and pediatric self-report responses ($r_s = 0.65$, $p < 0.001$; $r_s = 0.72$, $p < 0.001$, respectively), pain ($r_s = 0.60$, $p < 0.001$) and general health ($r_s = 0.58$, $p < 0.001$). General health in the HCTD-group was significantly positively correlated to fatigue, in both parent proxy and pediatric self-report ($r_s = 0.66$, $p < 0.001$; $r_s = 0.7$, $p < 0.001$, respectively) and pain ($r_s = 0.72$, $p < 0.001$). Pain in the HCTD-group was significantly positively correlated with fatigue, both in parent proxy and pediatric self-report responses ($r_s = 0.63$, $p < 0.001$, $r_s = 0.68$, $p < 0.001$, respectively).

Explorative analysis in the HCTD-subgroup MFS showed that disability was moderately significantly positively correlated to fatigue reported by parent proxy and general health ($r_s = 0.39$, $p= 0.004$; $r_s = 0.33$, $p = 0.031$, respectively). In the HCTD-subgroup hEDS, disability was highly significantly positively correlated to fatigue reported by parent proxy, pain and general health ($r_s = 0.74$, $p < 0.001$; $r_s = 0.67$, $p < 0.001$; $r_s = 0.65$, $p = 0.004$, respectively).

Discussion

This is the first quantitative, multicenter survey study to report on the burden of disease in childhood HCTD. Compared to normative data, children and adolescents with HCTD and HCTD-subgroups MFS, LDS, EDS and hEDS reported increased fatigue, pain, disability and decreased general health, with most differences translating into very large-sized effects.

These results match our previous qualitative studies on children and adolescents with MFS [9, 10] reporting on limitations in activities and participation, and descriptive studies in children with MFS, EDS and hEDS reporting on fatigue, pain and the negative impact on daily (physical) functioning. [7, 11-17, 20] Our results are also in line with studies using standardized validated measures in children with hEDS and HSD reporting on increased fatigue and pain, [18] generalized hyperalgesia [21] and disability. [17]

To interpret whether our data's large effect sizes are clinically relevant, we referenced our data to effect size/minimal clinically important difference (MCID) benchmarks and the reported MCIDs of the used questionnaires in this study. Although MCID, defined as the smallest (absolute) difference in score that patients perceive as beneficial, is mainly used to evaluate interventions, it might also indicate clinical relevance. One of the distribution based calculations of an MCID uses a cut-off point of Cohen's $d = 0.5$. [38] In our data, most differences translated into very large-sized effects, suggesting meaningful data. Moreover, the previously published MCID of the CHAQ-DI (median score 0.13) [35, 39] and PROMIS pediatric self-report (three points on the PROMIS T-score scale) [40] suggest that fatigue and disability in our study are clinically relevant in the HCTD-group and HCTD-subgroups EDS and hEDS.

The most adverse sequels were reported in children with hEDS, whereas the least were reported in those with MFS. In previous qualitative studies, children and adolescents with MFS showed the ability to use productive coping strategies. [9, 10] Articles on coping strategies in children with hEDS are lacking. A difference in coping strategies between the HCTD-subgroups might partially explain the results. Furthermore, participants with MFS, LDS and EDS were recruited by one of the expert centers Marfan syndrome and related (connective tissue) disorders in the Netherlands and Belgium. These participants receive medical care from a multidisciplinary team. Participants with hEDS were informed by the MFS and EDS patient associations and contacted the research team themselves if they were interested in participating in the study. Problems in the daily life of children with hEDS might therefore not have been discussed or treated in a clinical setting. This might contribute to further deterioration of physical functioning. [20]

This new knowledge calls for systematic monitoring and standardized questionnaire assessments of fatigue, pain, disability and general health in the HCTD-group and HCTD-subgroups. Physical therapy, psychological counselling [18] and a multidisciplinary rehabilitation program [17] were reported as helpful in children and adolescents with hEDS and HSD. [18] This also indicates the importance of standardized physical assessments and tailored physical interventions in clinical care according to the Frequency, Intensity, Type and Time (FITT) factors [41] combined with lifestyle/sports education and psychosocial support.

A strength of our study is that a large sample of children with HCTD was included in our study. Furthermore, participants were recruited from one of the expert centers Marfan syndrome and related (connective tissue) disorders in the Netherlands, including the University Medical Centers of Amsterdam, Leiden, Groningen, Maastricht and Nijmegen, and at the Center for Medical Genetics of the Ghent University Hospital in Belgium. These countries have similar cultures and the surveys in Dutch and Belgium–Flemish are comparable.

Our results must also be viewed within the limitations of the study. First, the sample sizes of the HCTD-subgroups EDS and LDS were small, and the explorative results should be interpreted with caution. In future, to demonstrate more subtle differences among HCTD-subgroups, a large European study with the cooperation of the European Reference Network (ERN) Skin, Mendelian Connective Tissue Disorders and ERN VASCERN could increase the sample size. Second, the children's medical diagnosis was parent-reported. Our study design did not allow for checking the children's medical diagnosis or clinical features. In 2017, the international clinical criteria for hEDS were revised, allowing for a better distinction from other joint hypermobility disorders. [3]

Although our data were gathered in 2020, it is plausible that children with hEDS were not re-diagnosed and some might consequently not meet the 2017 hEDS criteria.

Conclusions

Children and adolescents with HCTD reported increased fatigue, pain, disability and decreased general health compared to normative data, with most differences translating to clinically relevant and very large-sized effects. The most adverse sequels were reported in children with hEDS, whereas the least were reported in those with MFS. This new knowledge calls for systematic monitoring and standardized assessments of fatigue, pain, disability and general health, not only through questionnaires but also physical assessments, and tailored interventions in clinical care.

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CHAPTER 6

"Me and my friends riding a sleigh in the snow" by Milou Bron (8 years)

Heritable Connective Tissue Disorders in childhood: Decreased health-related quality of life and mental health

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Abstract

Objectives: 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.

Study design: This observational multicenter study included 126 children, aged 4 - 18 years, with Marfan syndrome (MFS, n = 74), Loeys-Dietz syndrome (LDS, n = 8), molecular confirmed Ehlers-Danlos syndromes (EDS, 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 (SDQ).

Results: Compared to a representative general population sample, parent-reported HRQoL of the HCTD-group showed significantly decreased Physical sum scores ($p < .001$, $d = .9$) and Psychosocial sum scores ($p = .024$, $d = .2$), indicating decreased HRQoL. Similar findings were obtained for child-reported HRQoL. The parent-reported mental health of the HCTD-group showed significantly increased Total difficulties sum scores ($p = .01$, $d = .3$), 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.

Conclusions: 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.

Introduction

Heritable Connective Tissue Disorders (HCTD) are characterized by pathological connective tissue fragility and multisystemic involvement. [1-5] The phenotypes of the most common HCTD, Marfan syndrome (MFS), [2, 3] Loeys-Dietz syndrome (LDS) [4] and Ehlers-Danlos syndromes (EDS) [5] are based on clinical criteria and molecular confirmation. Hypermobile EDS (hEDS) is an exception because the genetic cause has not yet been determined. [5] HCTD show similarities in cardiovascular, musculoskeletal and cutaneous features that can evolve in childhood. [1] In addition, children and adolescents with HCTD report increased pain and fatigue, decreased general health, and limited activities and participation, compared to their healthy counterparts. [6-11] Such problems, in turn, have been found to evoke behavioral and emotional problems in children with chronic illnesses. [12, 13] 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. [14]

There are few studies on HRQoL of children with HCTD. In a review on psychosocial outcomes of MFS [15] self-reported HRQoL was decreased in two studies, [16, 17] and unimpaired in another study. [18] HRQoL was also decreased in children with EDS, [17] hEDS [5] and Hypermobile Spectrum Disorder (HSD), [5] the current label for patients with joint hypermobility and musculoskeletal problems who do not meet the 2017 international clinical criteria for hEDS. [10, 19] To 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. [15, 20] Moreover, adults with hEDS and HSD reported decreased physical and psychosocial HRQoL. [21-26]

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. [27] In addition, children with hEDS and HSD reported psychiatric disorders, most commonly anxiety and depression, in 41.3%. [10] 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. [28] Furthermore, adults with EDS, hEDS and HSD reported an increased risk of psychiatric disorders. [25, 29-37]

The current 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.

Materials and methods

Study design

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

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 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. 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.

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 in years, M (SD)	10.5 (4.0)	10.4 (4.1)	11.0 (3.6)	12.1 (4.3)	10.0 (3.7)

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

Measures

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.

Parent-reported Child HRQoL

Parent-reported Child HRQoL and parental and family impact were assessed with the parent-reported CHQ-PF50. [38, 39] The parent-reported CHQ-PF50 is normed for ages 5-18 and comprises Physical and Psychosocial sum scales and 12 subscales [see Table 2]. Of these 12 subscales, eight 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. [38, 39]

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, eight scales investigate the child's HRQoL and two scales investigate family activities and cohesion. The CHQ-CF45 does not include sum and subscales. [38, 40, 41]

For both CHQ questionnaires, a four-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. [38-41] Psychometric properties have also been established for the Dutch version. [39, 40]

Mental health

Mental health was assessed with the parent-reported SDQ. [42-45] 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. [42, 43] The SDQ is a widely used rating scale with well-studied and excellent psychometric properties. [42] Psychometric properties have also been established for the Dutch version. [43]

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 analysis 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. [46]

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 to representative general population samples. More specifically, the CHQ-PF50 data of our sample were compared to a representative United States (US) population sample of 391 children, aged 11.5 (SD 3.7) years, [38] the CHQ-CF45 data to a representative US population sample of 1438 children, aged 12.5 (SD 3.1) years, [38] and the SDQ data to a representative Dutch general population sample of 980 children, aged 10.7 (SD 4.5) years. [43] 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 analysis. The sample characteristics age and sex of the HCTD-group and the MFS- and hEDS-subgroups were compared to the representative samples using Chi-square tests and t-tests, respectively.

Subsequent analysis involved two steps. First, sum scores and subscale scores derived from the three questionnaires of the HCTD-group were compared to 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 analysis 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 [38] (p=.007), CHQ-CF45 [38] (p=.004) and the SDQ [43] (p=.007). Therefore, analysis 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. [47] 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 ≤ .05 was considered statistically significant. To control for multiple testing, the analysis of the subscale scores used a p-value of ≤ .001 to determine statistical significance.

Results

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 analysis. 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.

Child HRQoL

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 US representative general population sample.

Compared to the US 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 analysis 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 [see 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 [see Table 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.

Parent-reported parental and family Impact of the HCTD-group

Further analysis on parental and family impact showed significantly lower scores on subscales Parental Impact-Emotional and Family Activities compared to the US 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 actvities [see Table 2].

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 US representative general population samples.

On the CHQ-PF50, both, males and females with MFS obtained significantly lower Physical sum scores compared to scores of the US samples. No differences were found for the Psychosocial sum scores compared to scores of the US sample. Further analysis 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 ($p < .001$, $d = 2.2$) and Psychosocial ($p = .001$, $d = .4$) sum scores compared to the scores of the US sample. These results were explained by significantly lower scores on the subscales Physical Functioning ($p < .001$, $d = 1.0$), Role/Social-Emotional/Behavior ($p < .001$, $d = .7$), Role/Social-Physical ($p < .001$, $d = 1.0$), Bodily Pain ($p < .001$, $d = 1.0$), Mental Health ($p < .001$, $d = .6$), Self Esteem ($p < .001$, $d = .5$), General Health Perceptions ($p < .001$, $d = .7$) [see Table 2]. 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.

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

CHQ-PF50	HCTD (n=117)	US 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	***<.001***	**.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	***.024***	**.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	***<.001***	**.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	***<.001***	**.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	***<.001***	**.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	***<.001***	**.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	*.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	***<.001***	**.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	***<.001***	**.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	***<.001***	**.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	***<.001***	**.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	*.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	***<.001***	**.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	*.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

Table 2. Continued

CHQ-CF45	HCTD (n=89)	US 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	***<.001***	**.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	***<.001***	**.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	***<.001***	**.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	***<.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	*.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	***<.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	*.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	***<.001***	**.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	*.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	*.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

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.

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.

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

Compared to the US 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 ($p < .001$, $d = .4$) and limitations in their personal time ($p < .001$, $d = .4$). The impact on family was not significantly different of parents of the male and female MFS- and hEDS-subgroups compared to the US 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 [see Table 2 and 3].

Child-reported Child HRQoL of the HCTD-group

Compared to scores of the US 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 [see Table 2].

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.

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 to scores of the US sample. In addition the female MFS-subgroup obtained a significantly lower scale score on Bodily Pain [see 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 ($p < .001$, $d = 1.7$), Role/Social Emotional/Behavior ($p < .001$, $d = .8$), Role/Social-Physical ($p < .001$, $d = 1.6$), Bodily Pain ($p < .001$, $d= 2.0$), Mental Health ($p < .001$, $d = 1.0$), Self Esteem ($p < .001$, $d = .4$), General Health Perceptions ($p < .001$, $d = 1.6$), and Family Activities ($p < .001$, $d = .6$) compared to the scores of the US sample [see Table 2]. 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.

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.

Mental health

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 to 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 to 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, findings indicate decreased mental health of children with HCTD, which manifests in internalizing and emotional symptoms.

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 US representative general population samples.

CHQ-PF50	**MFS male (n=52)**	**US norm male (n=212)**	**MFS male vs norm p-value**	**Effect size Cohen's d**	**MFS female (n=22)**	**US norm female (n=177)**	**MFS female vs norm p-value**	**Effect size Cohen's d**
Scales (M (SD); range)								
Physical	48.1 (10.8); 11-60	52.4 (10.3); .5-64	***.01***	**.4**	46.4 (10.7); 17-60	54.9 (6.0); 28-65	***<.001***	**1.0**
Psychosocial	50.5 (7.4); 28-63	50.7 (4.9); 16-64	*.81*		50.6 (9.2); 22-64	51.9 (8.7); 7-65	*.51*	
subscales								
Physical Functioning	85.9 (18.5); 22-100	94.9 (17.0); 0-100	***<.001***	**.5**	83.6 (19.1); 17-100	97.9 (6.9); 61-100	***<.001***	**1.0**
Role/Social Emotional/ Behavioral	91.0 (20.0); 22-100	91.4 (20.8); 0-100	*.83*		88.8 (21.1); 33-100	93.9 (15.6); 0-100	*.17*	
Role/Social-Physical	90.9 (21.0); 0-100	92.5 (23.3); 0-100	*.65*		85.3 (19.2); 17-100	95.1 (14.7); 0-100	*.01*	
Bodily Pain	77.2 (20.4); 10-100	82.8 (19.2); 19-100	*.06*		69.6 (23.9); 0-100	80.3 (18.9); 0-100	*.02*	
Behavior	77.3 (14.9); 43-100	74.1 (16.3); 25-100	*.20*		76.7 (14.9); 47-100	77.5 (17.0); 0-100	*.75*	
Mental Health	75.6 (12.2); 50-100	79.6 (13.2); 20-100	*.05*		73.8 (12.5); 45-90	77.1 (13.2); 20-100	*.27*	
Self Esteem	73.5 (12.7); 38-100	79.6 (17.7); 0-100	*.02*		73.1 (17.0); 25-100	79.9 (17.4); 25-100	*.09*	
General Health Perceptions	61.1 (16.5); 18-96	71.6 (18.1); 8-100	***<.001***	**.6**	63.8 (15.2); 27-96	74.7 (16.3); 23-100	***<.001***	**.8**
Parental Impact-Emotional	71.8 (20.3); 8-100	78.0 (20.6); 0-100	*.05*		79.1 (21.0); 8-100	82.9 (16.9); 21-100	*.18*	
Parental Impact-Time	88.6 (15.1); 44-100	85.8 (21.5); 0-100	*.38*		85.2 (30.1); 0-100	90.7 (16.4); 11-100	*.19*	
Family Activities	86.5 (15.2); 42-100	88.9 (20.5); 0-100	*.45*		88.4 (19.1); 29-100	91.0 (15.7); 20-100	*.48*	
Family Cohesion	69.5 (22.8); 0-100	73.4 (21.2); 0-100	*.24*		74.3 (23.3); 0-100	70.9 (22.2); 0-100	*.48*	
CHQ-CF45	**MFS male (n = 35)**	**US norm male (n = 718)**	**MFS male vs norm p-value**	**Effect size Cohen's d**	**MFS female (n= 16)**	**US norm female (n = 720)**	**MFS female vs norm p-value**	**Effect size Cohen's d**

Table 3. Continued

Scales (M (SD); range)					
Physical Functioning	85.6 (18.1); 19-100	94.5 (12.8); 0-100	***<.001***	**0.9**	
Role/Social Emotional/ Behavioral	87.3 (19.4); 22-100	92.1 (17.1); 0-100	*.11*		
Role/Social-Physical	92.6 (14.3); 40-100	96.3 (14.0); 0-100	*.13*		
Bodily Pain	77.9 (20.4); 21-100	84.3 (18.9); 0-100	*.04*	**0.8**	
Behavior	74.6 (15.3); 29-100	70.6 (19.4); 4-100	*.23*		
Mental Health	65.8 (8.5); 42-79	79.0 (13.3); 11-100	***<.001***	**1.2**	
Self Esteem	79.7 (11.0); 48-100	81.3 (19.0); 0-100	*.62*		
General Health Perceptions	70.0 (19.9); 27-100	79.6 (16.7); 5-100	***<.001***	**1.1**	
Family Activities	90.7 (13.1); 36-100	85.5 (21.9); 0-100	*.16*		
Family Cohesion	80.0 (17.2); 35-100	75.3 (22.7); 0-100	*.23*		

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.

The percentage of children of the HCTD-group with parent-reported scores above the clinical cut-off on the Total difficulties sum scale was significantly higher than the Dutch sample (9.5% vs. 19.2%, p = .001). Furthermore, a significantly higher percentage of children of the HCTD-group obtained scores above the clinical cut-off on the Internalizing sum scale (9.3% vs. 16.7%, p = .011) and the subscales Emotional symptoms (9.1% vs. 23.3%, p < .001), Hyperactivity-Inattention (12.1% vs. 20.8%, p = .008) and Prosocial behavior (10.3% vs. 22.5%, p < .001). Thus, compared to 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.

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

The male and female MFS-subgroups, showed no significant differences compared to 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 cut-off was only significantly higher on the Prosocial behavior subscale compared to the Dutch sample (14.1% vs. %, 29.8, p < .001; 6.2% vs. 14.7%, p < .001, respectively).

The hEDS-subgroup obtained significantly higher scores on the Total difficulties sum scale compared to the representative general population sample, with this group difference translating into a small-sized effect (p < .001, d = .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 < .001, d = .9) but no group differences were found on the Externalizing sum scale. The hEDS-subgroup obtained higher scores on the subscales Emotional symptoms (p < .001, d = 1.3) and Hyperactivity-Inattention (p = .039, d = .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 to the Dutch sample, the percentage of children of the hEDS-subgroup with scores above the clinical cut-off was significantly higher on the Total difficulties sum scale (9.5% vs. 30.8%, p < .001); the Internalizing sum scale (9.3% vs. 30.8%, p < .001); and the subscales Emotional symptoms (9.1% vs. 42.3%, p < .001) and Hyperactivity-Inattention (12.1% vs. 30.8%, p = .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

Table 4 Mental health assessed with the parent-reported SDQ of the HCTD-group, subgroups and the US 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)	.83	9.1 (6.3); 0-25	.84	7.6 (5.7); 0-33	***.01***	**.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)	.73	4.4 (3.4); 0-16	.79	3.2 (3.2); 0-17	***<.001***	**.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)	.80	4.7 (4.0); 0-13	.77	4.4 (3.5); 0-19	*.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)	.73	3.0 (2.4); 0-10	.73	1.9 (2.0); 0-10	***<.001***	**.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)	.42	-	.54	1.2 (1.4); 0-10	-		-	-	-	-
Hyperactivity-Inattention(0-10)	.87	3.6 (3.3); 0-10	.82	3.3 (2.7); 0-10	*.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)	.61	1.4 (1.7); 0-8	.66	1.3 (1.7); 0-10	*.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)	.74	8.1 (2.1); 1-9	.72	8.1 (1.9); 0-10	*.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

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: MFS; n, number; p, probability; SD, standard deviation. Tables report M (SD) and range. Scales with internal consistency Cronbach's alpha < .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.

of clinical scores of internalizing symptoms, emotional symptoms, and hyperactivity-inattention problems.

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 to representative general population samples, with most adverse outcomes in children with hEDS and least in those with MFS. In addition, parents of children and adolescents with HCTD experience a significantly increased amount of distress and limited family activities.

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, [16, 17] EDS, [17] hEDS and HSD [10, 19, 48] and with studies on adults with HCTD. [15, 20-26]

In subsequent analysis 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 studies on children with hEDS and HSD who also reported decreased physical and psychosocial HRQoL. [10, 19] In addition, two studies on children with MFS reported decreased physical and psychosocial HRQoL [16, 17] and one study reported normal HRQoL. [18] 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. [6, 7, 11] It is of additional value to include the perspectives of both parents and children.

Change in Health

In our study, parents and children with HCTD, MFS (male and female) and hEDS report in around 1 of 5 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. [1, 3-5, 8, 48-50] Other studies also reported increased pain of children with HCTD which negatively influenced activities and participation in daily life. [8, 10, 51, 52] 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.

Parental and family impact

Parents of children with HCTD experience a significantly increased amount of distress and limited family activities compared to the US sample. Subsequent analysi s show that, compared to the US 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 mount of distress. Our previous study also showed comparable distress in parents of children with MFS compared to a representative general population. [11] 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. [7] 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. [14] Therefore medical professionals should be aware of the parental and family impact.

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, [10] an older study on children with MFS [27] as well as with studies on adults with EDS, hEDS and HSD. [25, 29-37] 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. [12, 13] As decreased mental health negatively influences daily life, we strongly recommend systemic monitoring mental health.

The subsequent analysis 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 [10] and studies on adults with EDS, hEDS and HSD reported an increased risk of psychiatric disorders. [25, 29-37] Interestingly, children (male and female) with MFS showed no significant differences on the SDQ scores compared to 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. [27] However, a review on adults with MFS reported co-occurrence of MFS and psychiatric disorders, but firm conclusions were not drawn. [28] 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.

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 to the data of a US representative general population sample normed for ages 5-18. Therefore, we had to omit CHQ-PF50 data from nine parents of 4-year-olds from the analysis. Second, there may be cultural differences between the Dutch-Flemish and US 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 of 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 US. [53] 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 [5] 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. 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.

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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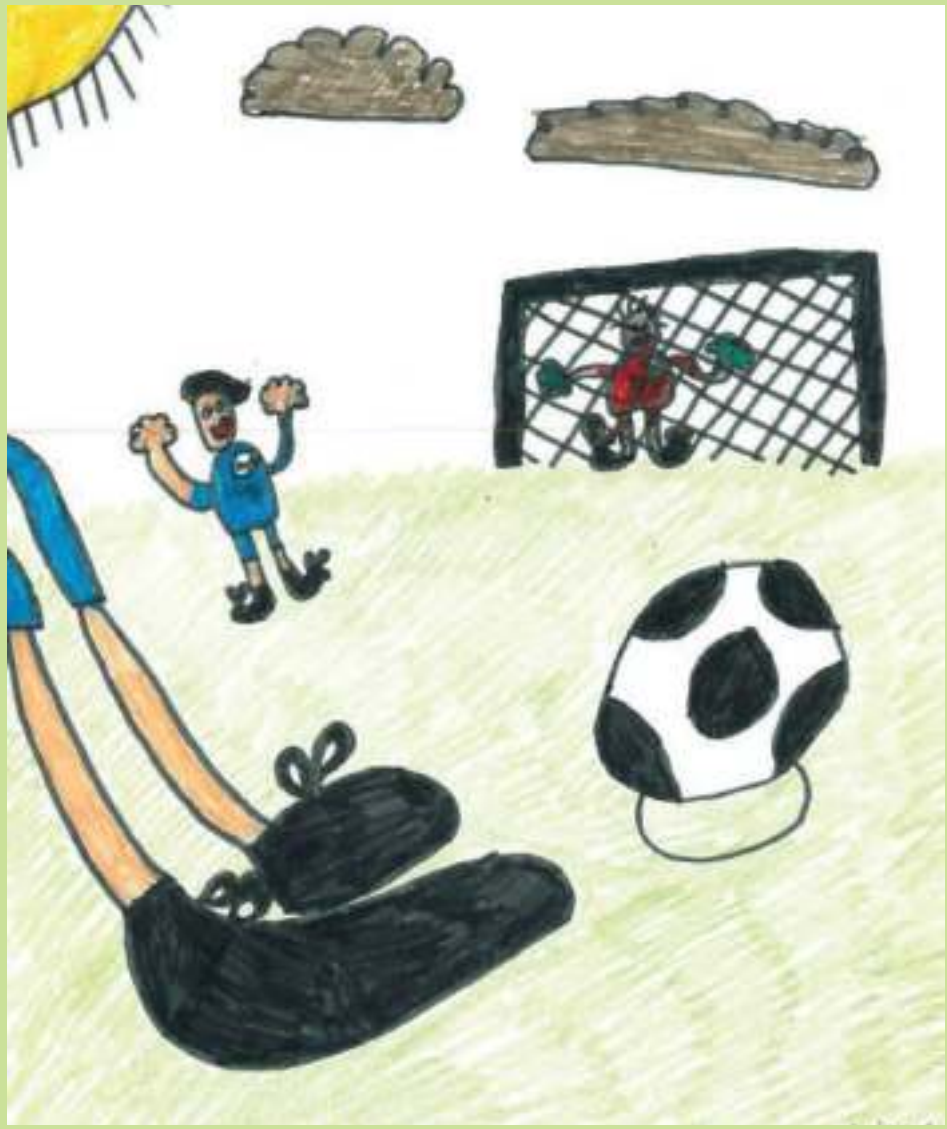
CHAPTER 7



"Me and my friends playing soccer" by Vince Zwemmer (10 years)

General discussion, conclusions and reflections on the main findings

The general discussion provides the overall conclusions of this thesis and discusses main findings in a broader perspective, including the methodological considerations. The implications for clinical care and directions for future research are outlined.

Part 1 Functioning and health of children and adolescents with Marfan syndrome, their parents and family

Functioning and health of children and adolescents with Marfan syndrome

In chapters 2 and 3, semi-structured interviews and focus groups identify that children (proxy-reported) and adolescents (self-reported) with MFS perceive problems in keeping up with peers in school, sports, leisure, friendships, relationships and work. In addition, they feel different from peers due to their perceived appearance, limited activities and participation. [1, 2] Both chapters report everyday problems on all domains of the "International Classification of Functioning, Disability and Health for Children and Youth" (ICF-CY), [11] as well as facilitating and limiting environmental and personal factors. This provides a better understanding of functioning and health of children and adolescents with MFS. [1, 2]

Our results are in line with a review that described the negative impact of MFS on physical characteristics, pain, fatigue and activities of children and adolescents. [3] In addition, children and adolescents with MFS are limited in participation in competitive and contact sports as recommended by the national and international MFS and cardiovascular guidelines. [3-10]

Environmental factors such as positive attitudes, relationships and support from parents, family, friends and teachers are reported by parents of children with MFS and adolescents with MFS to facilitate participation, in chapters 2 and 3. [1, 2] This is in line with a systematic review that concluded that positive support and relationships with peers significantly contributed to participation in daily life of adolescents with congenital or acquired disorders. [13] Furthermore, support of family helped adolescents with congenital heart diseases adopt positive perceptions toward participation in activities. [14] On the other hand, in chapters 2 and 3, negative support is reported to limit participation. [1, 2] This is consistent with a study on adults with MFS who experienced negative support to limit their participation. [15]

Personal factors, such as positive self-esteem, coping strategies, a healthy lifestyle, planning and the ability to express support needs are reported by parents of children with MFS and adolescents with MFS to facilitate participation as well, in chapters 2 and 3. On the contrary, negative perceived appearance and low self-esteem limited participation. [1, 2] This is in line with a study on adults with MFS who reported that negative body image, low self-esteem and introvert behaviour negatively affected their social lives. [15] Similarly, two meta-analyses on children with various chronic diseases (such as obesity, cystic fibrosis, scoliosis, asthma, growth hormone deficits, spina bifida, cancer and diabetes) showed that negative body image [16] and low self-esteem [17] hindered children's participation.

In order to understand functioning and health of children and adolescents with MFS, it is important to have knowledge of physical MFS characteristics, activities, participation, (facilitating and limiting) environmental and personal factors, and the interactions between domains.

Disease knowledge gaps of adolescents with MFS

In chapter 3, adolescents with MFS, report limited knowledge about the origin of MFS, MFS-related physical characteristics and the impact of MFS on daily activities and participation. [2] Knowledge gaps on disease were also reported in children and adolescents with chronic heart disease, [18, 19] asthma and epilepsy. [20] Education on the consequences of living with MFS facilitated adults to understand and cope better with the negative impact of MFS on their daily lives. [21] This implies that educational programs for children and adolescents with MFS can increase understanding and coping with the disorder, which can improve their functioning and health.

Distress and everyday problems in parents of a child with Marfan syndrome

In chapter 2, parents experience 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. [1] These results are in line with our expectations as parents of a child with MFS have to attend the hospital regularly for their child's medical follow up and [6, 7, 10] parents are aware of the risks of MFS related medical complications. [5, 22-24] Furthermore, parents of children with chronic diseases, cancer and congenital heart diseases showed greater parental burden compared to parents of healthy children due to similar problems reported in our studies. [25-31] In addition, the employment and wellbeing of parents caring for a chronically ill child were negatively affected. [32] They experienced poorer mental health such as distress, anxiety, depression, hopelessness and somatization symptoms, compared to parents of healthy children. [26, 33] Parents of a child with cancer, [34] mucopolysaccharidosis type III, [35] inflammatory bowel disease, [36] Down syndrome [37] and a chronic disease of any type, [38] all screened by the standardized, validated questionnaire Distress thermometer for Parents of a chronically ill child (DT-

P) [39, 40] also reported significantly higher distress and more often everyday problems compared to parents in the control group.

Surprisingly, in chapter 4, parents of a child with MFS report clinical relevant distress on the DT-P questionnaire in approximately one-third, which is not significantly different compared to parents of healthy children. This is an unexpected result given the parents' reports of increased burden in chapter 2 and 3 [1, 2] and the current literature on distress in parents of children with chronic diseases. [25-40] Parents may have felt more comfortable sharing everyday problems and distress in individual interviews and focus groups than in completing online questionnaires.

In addition, little is known about distress in parents with a heritable disorder. MFS is an autosomal dominant disorder caused by a pathogenic variant in *FBN1* [5] and occurs de novo in only a quarter of patients. Therefore, in many families, both a parent and one or more children are diagnosed with MFS. These parents may have experienced the negative impact of MFS on their own functioning and health [41-49] and may therefore have developed strong parental coping strategies. This is endorsed by a review on psychosocial factors in adults with MFS. The review reported that despite the psychologically distressing aspects of MFS, most adults exhibited above average life satisfaction due to efficient coping and self-efficacy. [47] On the contrary, adults with Heritable Connective Tissue Disorders (HCTD), including MFS, reported that their disorder negatively impacted family life, reproductive planning, physical activities, psychosocial functioning, education and work. [43-59] Studies of parents who are themselves chronically ill also reported adverse effects on their Health-Related Quality of Life (HRQoL) [29, 60] and a tendency toward limited social and family life. [61] Therefore, health professionals should be aware of clinical distress in parents of children with MFS.

Part 2 Functioning and health of children and adolescents with Heritable Connective Tissue Disorders

Pain, fatigue, activities and general health

Heritable Connective Tissue Disorders (HCTD): MFS, Loeys-Dietz (LDS), molecular confirmed Ehlers-Danlos syndromes (EDS) and hypermobile Ehlers-Danlos syndrome (hEDS) are all characterized by pathological connective tissue fragility, multi-systemic involvement and similar physical features. [4, 5, 50, 58, 62, 63] Chapter 5 reports increased pain and fatigue, and decreased activities and general health of children and adolescents with HCTD compared to representative general population samples. [64] These results not only indicate similarities in physical features but also in pain, fatigue, activities and general health that may impact functioning and health of children and adolescents with HCTD.

Our findings in chapter 5 match with the results of our previous qualitative studies in chapter 2 and 3 [1, 2] and descriptive studies on children and adolescents with MFS, EDS and hEDS that reported the negative impact of HCTD on physical features, pain, fatigue, activities and participation. [3, 7, 56, 59, 65-67]

To our knowledge, no quantitative studies, using standardized validated questionnaires on pain, fatigue, activities and general health, have been conducted in children and adolescents with MFS, LDS and EDS. Few quantitative studies on children and adolescents with hEDS and Hypermobile Spectrum Disorder [57] (HSD, the current label for patients with joint hypermobility and musculoskeletal problems who do not meet the clinical criteria for hEDS) are in line with our results. These studies reported increased pain and fatigue, [68] generalized hyperalgesia, [69] and decreased functioning which improved after following an outpatient multidisciplinary rehabilitation treatment program. [70]

In conclusion, our results in chapter 5 show increased pain and fatigue, limited activities and decreased general health of children and adolescents with HCTD which can impact their functioning and health.

Mental health in children and adolescents with Heritable Connective Tissue Disorders

Chapter 6 is the first to report decreased mental health of the total group of children and adolescents with HCTD compared to a representative general population sample. There are few studies on mental health in children with HCTD. An older study reported attention deficit disorder with or without hyperactivity in 17% of children with MFS. [71] Psychiatric disorders, most commonly anxiety and depression, were reported in 41.3% of children with hEDS/HSD. [68] To our knowledge, studies on mental health in children with LDS and EDS are not available.

A review on adults with MFS reported co-occurrence of MFS and psychiatric disorders but firm conclusions were not drawn. [72] Furthermore, studies on adults with EDS and hEDS reported an increased risk of psychiatric disorders. [73-82] Meta-analyses on children with long-term physical conditions showed increased anxiety and depression. [83-85] In addition, pain and fatigue in children with a chronic condition had a negative impact on mental health. [86]

It may be that HCTD related physical features, increased pain and fatigue, limited activities and participation, limiting environmental and personal factors, and decreased general health and HRQoL, negatively impact mental health in children and adolescents with HCTD.

Health-related quality of life in children and adolescents with Heritable Connective Tissue Disorders

Chapter 6 is the first to report decreased physical and psychosocial HRQoL of the total group of children and adolescents with HCTD compared to a representative general population sample. Decreased HRQoL of the HCTD-group manifests in increased pain, decreased physical functioning, general health, low self-esteem, limitations in school related and leisure activities and restricted participation. There are few studies on pediatric HRQoL within the separate HCTD-subgroups. HRQoL of children with MFS [47] was decreased in two, [87, 88] and unimpaired in another study. [89] HRQoL was also decreased in children with EDS [88] and hEDS/HSD. [68, 90] To our knowledge, there are no studies on HRQoL in children with LDS.

Adults with MFS, LDS, and EDS reported that their physical condition and cardiovascular problems had a negative impact on quality of life. [47, 91] Adults with hypermobile hEDS/HSD reported decreased physical and psychosocial HRQoL. [55, 59, 78, 92-94] In addition, children and adolescents with chronic conditions were more likely than others to experience multiple problems that could affect their quality of life. [95] Further, two systemic reviews on children with chronic diseases described that pain and fatigue had a negative impact on the HRQoL. [86, 96]

The results in chapter 6, our previous results in chapter 2, 3 and 5, [1, 2, 64] descriptive studies on the development of HCTD related physical features in childhood [5, 50, 51, 58, 62] and studies on increased pain and limitations in activities in adolescents with hEDS [67, 68, 70] all contribute to the knowledge of factors that impact HRQoL. These various studies support the idea that problems within all domains such as HCTD related physical features, increased pain and fatigue, limited activities and participation, limiting environmental and personal factors and decreased mental health can have a negative impact on HRQoL in children and adolescents with HCTD.

Differences in functioning and health between Heritable Connective Tissue Disorders

Pain, fatigue, activities and general health

In chapter 5, all HCTD-subgroups reported significantly increased pain, decreased activities and general health compared to representative general population samples. Interestingly, subsequent analysis show most problems of the hEDS-subgroup and least of the MFS-subgroup. [64] There may be differences in the severity of objectively measured physical characteristics for each HCTD-subgroup. Our studies did not comprise measures of body functions and structures.

Mental health

In chapter 6, subsequent analysis on mental health of HCTD-subgroups indicate decreased mental health of the hEDS-subgroup and normal mental health of the MFS-subgroup compared to a representative general population sample. This is in line with studies on adults with EDS and hEDS reporting an increased risk of psychiatric disorders. [73-77] A review on adults reported co-occurrence of MFS and psychiatric disorders but did not conclude decreased mental health. [72]

In chapter 5 the hEDS-subgroup report significantly higher levels of pain, fatigue, decreased activities and general health compared to the MFS-subgroup. [64] These differences in severity of physical features, activities and general health may partially explain the mental health problems in the hEDS-subgroup. Further, in chapter 6, the psychosocial HRQoL is decreased in the hEDS-subgroup whereas it is not in the MFS-subgroup. The level of psychosocial HRQoL may influence mental health. In addition, chapter 6 reports that the MFS-subgroup exhibits prosocial behaviors (the intention to help and share with others) which may protect them from decreased mental health.

Health-related quality of life

In chapter 6, subsequent analysis between HCTD-subgroups indicate decreased physical and psychosocial HRQoL in the hEDS-subgroup and solely decreased physical HRQoL in the MFS-subgroup compared to a representative general population sample.

The hEDS-subgroup reports increased bodily pain and limitations in school/leisure activities and participation with friends to contribute to decreased HRQoL whereas the MFS-subgroup does not report this. In line with this, chapter 5 reports significantly increased pain, fatigue and decreased activities of the hEDS-subgroup compared to the MFS-subgroup. [64] This may indicate that differences in severity of physical manifestations and limitations in activities between HCTD-subgroups contribute to differences in HRQoL. This is in line with a study on children and adolescents with hEDS [68] and a systemic review on children with chronic diseases that report that levels of general fatigue and pain are the best predictors of HRQoL. [96]

Furthermore, psychosocial HRQoL was decreased in the hEDS-subgroup and normal in the MFS group. This may be partially explained by the significantly lower reported (personal factor) "self-esteem" by the hEDS-subgroup. This is in line with a meta-analysis of children with various chronic diseases, in which low self-esteem negatively impacted social participation. [17] In addition, chapter 6 reported decreased mental health in the hEDS-subgroup and normal mental health in the MFS-subgroup. Decreased mental health may also contribute to decreased HRQoL as reported in a study on children and

adolescent with hEDS. This study reported that the presence of any psychiatric diagnosis was correlated with a lower HRQoL score. [68]

Environmental and personal factors

Facilitating and limiting environmental and personal factors may partially explain differences in functioning and health, HRQoL and mental health between HCTD-subgroups. Chapter 2 and 3 provide a better understanding of facilitating and limiting environmental and personal factors of children and adolescents with MFS. [1, 2] Environmental factors such as positive attitudes, relationships and support; and personal factors such as positive self-esteem, coping strategies, a healthy lifestyle, planning and the ability to express support needs facilitate participation in the daily lives of these children and adolescents with MFS. [1, 2] There is little knowledge on environmental and personal factors that influence the functioning and health of the other HCTD-subgroups.

In addition, children and adolescents with MFS, LDS and EDS are treated regularly within one of the expert centers Marfan syndrome and related (connective tissue) disorders in the Netherlands and Belgium by a multidisciplinary team. This is considered as a facilitating environmental factor. Children with hEDS are usually not treated within one of the expert centers. Therefore, the everyday physical and psychosocial problems of children and adolescents with hEDS may not be discussed or treated in a clinical setting, leading to further problems. This is in line with a study on adolescents with hEDS that reported that unidentified and untreated problems led to further deterioration of physical functioning and restriction of participation. [97]

New child and adolescent friendly model of Functioning and Health

In clinical care of children and adolescents with HCTD, it is highly important to explore, explain and discuss everyday problems and the outcomes on the standardized validated questionnaires on pain, fatigue, activities, participation, environmental and personal factors, HRQoL and mental health. Then, tailored interventions can be developed to optimize functioning and health.

Despite the increased use of the ICF-CY, there is criticism on the content of the present version of the ICF-CY and the applicability of the model. [98] First, disability is a derivative of functioning and therefore, in this thesis, we prefer to use the terms "Functioning and Health". Second, HRQoL is not integrated in the ICF-CY, although children and adolescents with chronic conditions are more likely than healthy peers to experience multiple problems that can affect their (HR)QoL. [95] The ICF-CY solely describes in a footnote (note 30, page 264) that quality of life deals with what people "feel" about their disorder/disease or its consequences; hence, it is a construct of "subjective well-being". [11] A modified version of the ICF was proposed including QoL but did not specify HRQoL. [95] Third, the ICF and the ICF-CY use exactly the same model to map functioning and health of children, adolescents and adults. Since children and adolescents are largely dependent on their parents and adults usually are not, the interactions between domains may be different. Fourth, in the ICF-CY model the domain "activities" is centered, which insinuates a greater importance of this domain. One study proposed modified versions of the ICF model. [98] In addition, the current ICF-CY model has a plain appearance. To our knowledge there is no modified ICF-CY model available which can be used in pediatric clinical care.

Therefore, I developed a new child and adolescent friendly model "Functioning and Health", with the advice of colleagues, children, adolescents and parents. This new model is inspired by the ICF-CY [11] and based on the knowledge from this thesis about pain, fatigue, activities, participation, HRQoL, mental health, facilitating and limiting factors and the interactions between domains. [1, 2, 64, 109] The "Functioning and Health" model can be used by physicians, psychologists, social workers, allied health professionals and nurses to explore, explain, and discuss the child's and adolescents functioning and health and the interactions between domains together with children, adolescents and their parents. This will lead to awareness and understanding and allows treatment options to be discussed. Tailored interventions can then be developed to optimize functioning and health of children and adolescents with HCTD.

This model may also be useful in clinical care of children and adolescents with other chronic disorders and diseases.

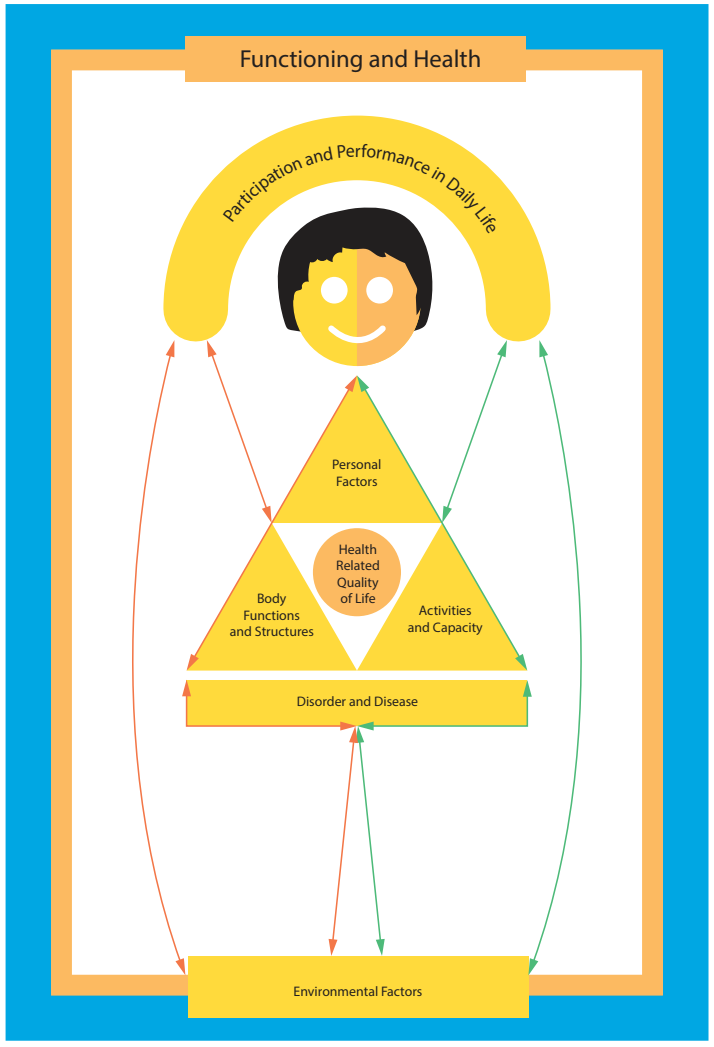


Figure 1. New child and adolescent friendly model "Functioning and Health". Green arrows indicate facilitating factors. Orange arrows indicate limiting factors. "Functioning" comprises all body functions, activities and participation; "Health" comprises complete physical, mental and social functioning; "Disorder and Disease" comprises physical and mental disorders and diseases; "Body Functions" are the physiological aspects of body systems; "Structures" are the anatomical support of the body; "Activity" is defined as the execution of a task or action; "Capacity" describes the person's ability to execute a task or an action; "Participation" refers to involvement in daily life; "Performance" describes what a person does in the environment; "Environmental Factors" are defined as the physical, social and attitudinal environment in which persons live and conduct their lives; "Personal Factors" comprise the particular background; "Health-Related quality of Life" is defined as the perceived (subjective) health related physical, mental, and social functioning. This new model is inspired by the International Classification of Functioning, Disability and Health for Children and Youth, developed by the World Health Organisation [11] and is based on the knowledge from the thesis "Functioning and Health of Children and Adolescents with Heritable Connective Tissue Disorders and their Parents" of Jessica Warnink-Kavelaars, Pediatric Rehabilitation Physician, Amsterdam UMC, location University of Amsterdam, Department of Rehabilitation Medicine, Amsterdam, The Netherlands . [1, 2, 64, 109]

Clinical relevance of our findings

To interpret whether the effect sizes of our study results are clinically relevant, we referenced our data to effect size/ minimal clinically important difference (MCID) benchmarks and the reported MCIDs of the questionnaires used. MCID is defined as the smallest (absolute) difference in score that patients perceive as relevant, and is mainly used to evaluate interventions. It also indicates clinical relevance. One of the distribution based calculations of a MCID uses a cut-off point of Cohen's d = .5. [101] In our data, most differences translate into moderate to very large-sized effects, suggesting meaningful outcomes. Moreover, previously published MCID of PROMIS pediatric measures (3 points on the PROMIS T-score scale) [102] and CHAQ-DI (median score 0.13) [103, 104] suggest that differences in fatigue and disability in our studies are clinically relevant in children and adolescents with HCTD.

Methodological considerations

At the start of this thesis, few studies described the impact of HCTD on functioning and health and the interactions between domains of children, adolescents, parents and family.

Qualitative research contributes to a comprehensive understanding of the adolescents and parents' perspectives on the impact of disease on functioning and health. [105, 106] The strength of our two qualitative semi-structured interview and focus group studies in chapters 2 and 3 is that both studies are the first to explore functioning and health and the interactions between ICF-CY domains in children and adolescent with MFS. Furthermore, the trustworthiness, credibility, content saturation and verification were guaranteed throughout the entire study periods. [1, 2, 107] These two studies must also be viewed in the light of some limitations. All participants had the Dutch nationality and were treated at the Amsterdam UMC expert center Marfan syndrome and related disorders. Nevertheless, we assume that the parental and pediatric reports apply to all children and adolescents with MFS and HCTD and their parents with comparable cultural backgrounds. [108]

The strength of the quantitative study in chapter 4, is that it is the first study on distress of parents (with and without MFS) of a child with MFS compared to a representative general population sample. The Dutch KLIK PROM-portal (www.hetklikt.nu) containing the standardized validated questionnaire DT-P was used to quantify the everyday problems and distress of parents. [109] PROM-portals are a patient friendly way to systematically monitoring everyday physical and psychosocial problems and issues by standardized validated questionnaires. [39, 40, 110] Moreover, discussing the outcomes collected by the KLIK PROM portal contribute positively to communication about psychosocial problems. [39, 40]

This study has some limitations. All parents were recruited from the Amsterdam UMC expert center for children with Marfan syndrome and related disorders. We assume that the parental and pediatric reports apply to all children and adolescents with MFS and HCTD and their parents with comparable cultural backgrounds. [108]

The strength of the quantitative studies, chapter 5 and 6, are that these are the first to report increased pain and fatigue, limited activities and decreased general health, mental health and HRQoL in a large sample of children and adolescents with HCTD, consisting of four HCTD-subgroups, compared to representative general population samples. Furthermore, participants were recruited from the expert centers Marfan syndrome and related (connective tissue) disorders in the Netherlands and the Center for Medical Genetics of the Ghent University Hospital in Belgium. These two countries have similar cultures and the surveys in Dutch and Belgium–Flemish are comparable. However, these two studies also have limitations. The sample sizes of the HCTD-subgroups EDS and LDS were small, and the explorative results should be interpreted with caution. Parent reports were used on the child's diagnostic status. Since most children were recruited by their own physician of one of the expert centers, we are convinced that this approach is valid.

Implications for clinical care, networks and registries

Implications for consultations

The findings of this thesis warrant the importance of identification of everyday problems, functioning and health, HRQoL and mental health of children and adolescents with HCTD and their parents. During consultations, the predefined set of open questions [1, 2] and the new child and adolescent friendly model "Functioning and Health" [see Figure 1], both inspired by the ICF-CY, [11] are useful. Health professionals, psychologists, social workers and HCTD-specialized nurses can implement this set of open questions and this new model to explore, explain and discuss the child's and adolescents' functioning and health together with children, adolescent and parents.

Implications for education

In chapter 3, adolescents with MFS, report limited knowledge about their disorder. [2] Education about HCTD can improve understanding and coping with HCTD and can facilitate participation in daily life. [21] This calls for educational programs for children and adolescents with HCTD, their parents, family members, friends and teachers.

Implications for systemic monitoring

Children and adolescents with HCTD show large physical and psychosocial changes during childhood. Systemic monitoring provides data-points in time and allows indicating development and direction of change over time. This will improve understanding of functioning and health of individual children and adolescents with HCTD. Therefore, we recommend yearly monitoring of functioning and health (pain, fatigue, activities, participation, environmental and personal factors, HRQoL and mental health) by standardized validated questionnaires.

School, sport and leisure participation are often explored by a non validated list of questions. Adding a validated participation questionnaire [112] such as the Participation and Environment Measure for Children and Youth (PEM-CY), a measure that evaluates participation in the home, at school, and in the community, alongside environmental factors within each of these settings, will be of great value. [113, 114]

In chapter 4, parents of a child with MFS report clinical relevant distress on the DT-P questionnaire in approximately one-third. This is not significantly different compared to parents of healthy children. Clinical relevant distress in parents can affect parenting. Therefore, we recommend systemic monitoring of distress in parents of a child with MFS and targeted support if indicated.

In addition, we recommend systemic monitoring within a web-based portal for Patient-Reported Outcome Measures (PROM portal) such as the KLIK portal (www.hetklikt.nu) which is easy to use by children, adolescents, parents and health professionals. [40, 41]

Implications for physical measurements

Our studies show that investigation of pain, fatigue, activities and general health with standardized validated questionnaires provides a good overview of subjective physical problems of children and adolescents with HCTD. [64] Subsequently, this calls for objective standardized physical measurements of cardiovascular, musculoskeletal and cutaneous systems. These measurements will contribute to understanding of the impact of HCTD-related physical manifestations on executing physical activities: the physical capacity of a child. In addition, knowledge on both, subjective physical problems and objective physical measurements, improves understanding of the interactions between domains of functioning and health and helps to unravel differences between capacity and performance in children and adolescents with HCTD [see Figure 1]. In addition, a HCTD-specific set of physical measurements will provide HCTD normative data and improve clinical reasoning and risk profiling.

We recommend that current HCTD-care within the expert centers will be complemented by standardized validated physical measurements of pain intensity, skin hyperextensibility and fragility, muscle strength, motoric development, executing activities, physical fitness and activity monitoring. In addition, children and adolescents with HCTD undergo major changes in their physical grow. Therefore, these physical

measurements should be performed systemically as part of a monitoring follow up care program similar to the Follow Me – multidisciplinary follow up care program of the Emma's Children's Hospital, Amsterdam UMC.

Implications for tailored interventions

Well-studied interventional studies to improve functioning and health are very sparse in children and adolescents with HCTD. [70] To improve functioning and health of children and adolescents with HCTD, both the expert centers Marfan syndrome and related (connective tissue) disorders, pediatric rehabilitation teams and allied health professionals must work together to develop and provide interdisciplinary tailored physical, psychosocial, support and educational interventions.

Implications for national and international medical care, networks and registries

This thesis shows that multidisciplinary teams are needed to provide specialized clinical care for children and adolescents with HCTD. In the Netherlands, pediatric expert centers Marfan syndrome and related (connective tissue) disorders consist of different compositions of health professionals (pediatric cardiologist, pediatric ophthalmologist, clinical geneticist, pediatrician, pediatric rehabilitation physician, orthopaedic surgeon, HCTD-specialized nurse, psychologist, social worker, pediatric physical therapist).

Pediatric rehabilitation physicians are specialized in the development and improvement of physical functioning and health of children and adolescents with congenital or acquired conditions. The pediatric multidisciplinary rehabilitation team (pediatric rehabilitation physician, pediatric physiotherapist, pediatric occupational therapist, pediatric speech therapist, social worker, and psychologist) is able to identify and prioritize everyday issues and problems that limits the child's and adolescents' activities and participation. These teams have knowledge of the ICF-CY domains and interactions between domains. Furthermore, they can perform appropriate clinimetrics and develop an interdisciplinary tailored intervention program, together with (allied) health professionals, children, adolescents and their parents.

Therefore, involvement of a pediatric rehabilitation physician, a multidisciplinary rehabilitation team and allied health professionals in the care of children and adolescents with HCTD is of great value. I recommend adding this pediatric rehabilitation expertise to all expert centers Marfan syndrome and related (connective tissue) disorders.

In addition, to improve medical care for children and adolescents with HCTD, collaboration between the Dutch expert centers Marfan syndrome and related (connective tissue) disorders is important in the areas of organisation of care, medical knowledge and exchange, education and research. The expert centers are all affiliated with the "Dutch Network Marfan and related disorders. Then, expert centers HCTD across Europe, are affiliated with the European Reference Networks (ERN) Skin, VASCERN, and ReCONNET. National and European collaboration should be further reinforced to optimize medical care for children and adolescents with HCTD.

Fortunately, there is an enormous change in information technology (IT) over the last years which enhances capabilities for collecting, integrating, analysing and sharing medical information worldwide. Currently the ERN Skin is building an European Registry for RAre Skin diseases (ERRAS) in which the genetic and phenotypic characteristics as well as the ICF-CY domains are included (https://ern-skin.eu). This registry will collect medical information on patients with rare skin disorders such as HCTD. Furthermore, the Dutch Network Marfan and related disorders is supported by the overarching Dutch patient association for rare and genetic disorders in building a new educational website on MFS and related disorders (https://Marfan-expertise.net). This website will be available at the beginning of 2023 for medical professionals and patients and will provide information and education on MFS, interventions and research.

In conclusion, collaboration of national and international networks, registries and websites supported by IT can optimize awareness, knowledge, transparency and medical care for children and adolescents with HCTD.

Directions for future research

Qualitative research

The semi-structured interviews and focus groups in chapter 2 and 3 contribute to a comprehensive understanding on everyday problems and issues, functioning, health and support needs within the ICF-CY domains of children and adolescents with MFS, parents and family. [1, 2] Qualitative research can explore and provide better understanding of facilitating and limiting environmental and personal factors, interactions between domains and functioning and health of HCTD-subgroups [see Figure 1].

Longitudinal quantitative studies

The observational cross-sectional, multicenter studies in chapter 4, 5 and 6 contain cross-sectional data. [64, 109] Longitudinal studies provide several data points in time and direction of change over time. Therefore, longitudinal questionnaire and physical measurement studies will contribute to better understanding of different trajectories of functioning and health with its predictors of the total group of children with HCTD, HCTD-subgroups and individual children and adolescents with HCTD.

Interventional studies for children and adolescents with HCTD

Interventional studies to improve functioning and health are very sparse in children and adolescents with HCTD. [70] The results of this thesis call for the development of inter-professional interventional physical-, psychosocial-, educational- and support studies to improve functioning and health of children and adolescents with HCTD. Interventional studies should preferably focus on improving not one but multiple aspects of functioning and health. Physical interventions should be aimed at improving the child's physical fitness (HIT program), muscle strength (Power program), motor development and activities. Psychosocial interventions should focus on improving personal factors such as the child's coping styles, lifestyle, self-esteem and planning. Educational interventions should focus on improving knowledge about HCTD among children, adolescents and their parents, friends, and teachers. Support interventions should be aimed at improving environmental factors such as support from parents, friends, teachers and the child's participation in daily life.

Interventional studies for parents

Our studies in chapter 2 and 5 demonstrate a major impact of having a child with MFS on parental daily lives. This may also apply to parents of a child with other HCTD. For parents who need support, we recommend developing psychosocial, educational and support interventions to better cope with daily problems, organization of family schedules, social/leisure activities and work.

Dutch, European and global research collaboration

The collaboration of national (Dutch Network Marfan and related disorders) and international (European Reference Networks Skin, VASCERN and ReCONNET) networks, registries and websites can facilitate future studies with larger patient groups with a rare disorder such as HCTD. Subsequently, new treatments and interventions can be developed to improve medical care and the functioning and health of every child and adolescent with HCTD worldwide. The use of European and global registries will be of great value.

Upcoming results of the Follow You research program

This thesis is part of a 5 year research program "Follow You – a follow up program on physical, psychosocial functioning and participation in children and adolescents with (Heritable) Connective Tissue Disorders" supported by SIA RAAK-PRO, part of the Dutch Organisation for Scientific Research (NWO; SVB.RAAK>PRO02.007). Our Follow You research team will soon publish data on objective physical measurements and the results of an interventional multidisciplinary treatment program to improve functioning and health of children and adolescents with HCTD. The new knowledge from this thesis and the results of the Follow You research program will be implemented into a multidisciplinary follow-up care program. Furthermore physical-, psychosocial-, educational- and support interventions will be developed. To this end, functioning and health of children and adolescents with HCTD and their parents will be optimized.

The knowledge from this thesis and the Follow You research program about functioning and health can also be transferred to multidisciplinary follow-up care programs and interventions for children and adolescents with other chronic diseases.

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CHAPTER 8

"Me and my schoolmates" by Eva-Lynn (11 years)

Summary

Heritable Connective Tissue Disorders (HCTD) are characterized by pathological connective tissue fragility and multisystem involvement. The phenotypes of the most common HCTD Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and Ehlers-Danlos syndromes (EDS) show similarities in musculoskeletal, cardiovascular, and cutaneous features that can evolve in childhood. At the start of this thesis it was unclear to what extent children and adolescents with HCTD experience decreased functioning and health, and whether there is a difference among HCTD-subgroups. Therefore, the objective of this thesis is to explore and investigate functioning and health, including Health-Related Quality of Life (HRQoL) and mental health of children and adolescents with HCTD and their parents.

Chapter 1 presents a general introduction to HCTD, the current literature on functioning and health of children with chronic diseases and HCTD as well as distress in parents. In addition, national and international clinical care of children and adolescents with HCTD is outlined. The ICF-CY model is explained and definitions are provided.

Globally, over the past three decades, the prevalence of chronic diseases and aggregated disability in children and adolescents has increased. Pediatric chronic diseases can negatively impact functioning and health. Few studies described the negative impact of pediatric HCTD on pain, fatigue, activities and participation.

In the Netherlands, clinical care for children and adolescents with HCTD is centralized within the expert centers Marfan syndrome and related (connective tissue) disorders, all of which are affiliated with the "Dutch Network Marfan and related disorders". In this care, the involvement of a pediatric rehabilitation physician, a multidisciplinary rehabilitation team and allied health professionals is of great value. In Europe, the expert centers are affiliated with the European Reference Networks (ERN) SKIN, VASCERN, and ReCONNET.

Furthermore, the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY), developed by the World Health Organization (WHO) is explained and definitions are provided.

Part 1 Functioning and health of children and adolescents with Marfan syndrome, their parents and family

Chapter 2 describes the perspectives of parents regarding the impact of MFS on physical functioning, activities, participation, external and personal factors of children with Marfan syndrome aged 4 to 12 years. In addition, the study describes the impact of parenting a child with MFS on daily lives of parents and family.

In this qualitative study, 26 parents participated in individual semi-structured interviews and three focus groups. Interviews were guided by a newly developed set of open questions inspired by the ICF-CY. Audio recordings were transcribed, coded and analyzed using thematic analysis.

MFS related problems were reported within all ICF-CY domains. Identified themes were "difficulty keeping up with peers" and "being physically different and feeling different compared to peers". Parents reported that their child could not keep up with peers because of physical problems, pain, fatigue, and activity limitations. Children had difficulty in walking, running, cycling, dressing, throwing, writing, and handling cutlery. Children also experienced participation restrictions in school, sports, play, and other leisure activities such as parties, forest walks, amusement park visits, and holidays. In addition, parents reported that their children also felt different from their peers due to physical characteristics (such as excessive growth, long fingers, abnormalities of back, chest, knees, and feet) and limitations in social and physical activities. Furthermore, parents reported hurtful comments from the environment regarding appearance, play and sports.

Parents perceived a large impact of parenting a child with MFS on their own lives due to high care needs of their child, concerns about the development of their child as well as the lack of support and a limited social life.

Regarding the impact on family, parents reported that multiple family members with MFS, complex family schedules and regular adjustments of these schedules due to pain, fatigue, or illness of one of the family members contributed to increased family burden. Family cohesion and caring for each other were perceived as positive factors.

In conclusion, parents perceive a large impact of MFS on functioning and health of their children with MFS, on their own lives and of their families. The newly developed set of open questions, inspired by the ICF-CY can be useful during consultations and interviews with parents to explore functioning and health of their young children.

Chapter 3 describes the perspectives of adolescents regarding the impact of MFS on physical functioning, activities, participation, personal and external factors. It also describes the reported necessity for general support needs.

In this qualitative study, 19 adolescents with MFS, aged 12 to 18 years were interviewed. Interviews were guided by a newly developed set of open questions inspired by the ICF-CY. Audio recordings were transcribed, coded, and analyzed using thematic analysis.

MFS related problems were reported within all ICF-CY domains. Identified themes were "difficulty keeping up with peers" and "being physically different and feeling different from peers". Adolescents had trouble keeping up with peers in school, sports, work, leisure and friendships and relationships. They often could not physically meet the demands of after school jobs and work. In addition, adolescents with MFS felt that they differed from peers by their MFS related appearance and limitations in activities and participation. Supporting environmental factors such as "positive support from parents, friends, and teachers", "assistance or aids," and "environmental adaptations" were reported to facilitate their participation in sports, school, and leisure activities; having no or negative support was perceived to limit participation. Personal factors such as "positive coping strategies", a "healthy lifestyle", "being able to ask for help", and "good planning" were reported to improve their participation. In contrast, "feeling different" and "low self-esteem" were perceived as personal barriers.

In conclusion, adolescents experience a large impact of MFS on their functioning and health. The newly developed set of open questions inspired by the ICF-CY can be useful during consultations and interviews with adolescents to explore their functioning and health.

Chapter 4 focuses on distress and everyday problems of parents (with and without MFS) of a child with MFS.

This quantitative study investigated distress in 42 mothers (29% MFS) and 25 fathers (60% MFS) using the validated screening-questionnaire "Distress thermometer for Parents of a chronically ill child" (DT-P). Data were compared to a representative general population sample. No differences in percentages of clinical distress were reported between mothers and control-group mothers, fathers and control-group fathers and other groups. Distress was not associated with the children's MFS related characteristics.

In conclusion, parents of a child with Marfan syndrome reported clinically relevant distress in approximately one third. This is comparable to parents of healthy children.

Part 2 Functioning and health of children and adolescents with Heritable Connective Tissue Disorders

Chapter 5 investigates the prevalence and severity of fatigue, pain, activity limitations and general health of children and adolescents with HCTD using standardized validated questionnaires.

This observational, cross-sectional, multicenter study included 107 children, aged 4 to18 years, with MFS, n = 62 (58%), LDS, n = 7 (7%), EDS, n = 9 (8%) and hEDS, n = 27 (27%). The assessments included PROMIS Fatigue Parent Proxy and PROMIS Pediatric self-report, pain and general health Visual-Analogue-Scales (VAS) and Childhood Health Assessment Questionnaire (CHAQ).

Compared to representative general population samples, the total HCTD-group showed significantly increased fatigue and pain, activity limitations and decreased general health. Subsequent analysis of the HCTD-subgroups showed significantly increased pain, activity limitations, and decreased general health compared to representative general population samples. The hEDS- and EDS-subgroups additionally reported significantly higher severe fatigue. The most adverse results were reported in children with hEDS, whereas the least were reported in those with MFS. Activities showed significant relationships with fatigue, pain and general health. Most of the differences in this study translated into very large effect sizes.

In conclusion, compared to representative general population samples, the total group of children and adolescents with HCTD reports increased fatigue and pain, activity limitations and decreased general health. Most adverse results are reported in children with hEDS and least in those with MFS. Our results call for systemic monitoring of pain, fatigue, activities and general health of children and adolescents with HCTD with standardized validated questionnaires. The outcomes should be discussed during consultations.

Chapter 6 investigates HRQoL and mental health of children and adolescents with HCTD using standardized validated questionnaires.

This observational, cross-sectional, multi-center study included 126 children, aged 4-18 years, with MFS, n = 74 (59%), LDS, n = 8 (6%), EDS, n = 15 (12%) and hEDS, n = 29 (23%). 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 (SDQ). Scale scores and the percentage of

clinical scores of the total HCTD-group and HCTD-subgroups were compared to those of representative general population samples.

Compared to a representative general population sample, parent-reported HRQoL of the total HCTD group showed significantly decreased Physical Summary scores and Psychosocial Summary scores, indicating decreased total HRQoL. Similar findings were obtained for child-reported HRQoL. Subsequent analysis showed decreased HRQoL in both the hEDS- and the MFS-subgroups.

The parent-reported mental health of the total HCTD group showed significantly increased Total difficulties scores, indicating decreased mental health. Subsequent analysis showed decreased mental health in the hEDS-subgroup and normal mental health the MFS-subgroup.

In conclusion, the total group of children and adolescents with HCTD reports decreased HRQoL and mental health. Most adverse results are reported in children with hEDS and least in those with MFS. Our findings call for systemic monitoring of HRQoL and mental health of children and adolescents with HCTD with standardized validated questionnaires. The outcomes should be discussed during consultations.

Chapter 7 presents the overall conclusions of the individual studies in this thesis and discusses key findings in a broader perspective regarding clinical relevance of the findings, methodological considerations, implications for clinical care and directions for future research.

This thesis presents decreased functioning and health of children and adolescents with HCTD compared to representative general population samples. In addition, it provides further insight into the interactions between domains, and (facilitating and limiting) environmental and personal factors. Most adverse results are reported in children with hEDS and least in those with MFS.

The results of this thesis call for systematic monitoring of pain, fatigue, activities, participation, environmental and personal factors, HRQoL and mental health by standardized validated questionnaires. In addition, the current clinical care would benefit from a HCTD-specific set of objective physical measurements of pain, joints, skin, muscle strength, physical fitness, motor development and activity monitoring. This will contribute to HCTD normative data, clinical reasoning and risk profiling of children and adolescents with HCTD.

Interventional studies to improve functioning and health are very sparse. The findings of this thesis and the Follow You research program can be used to develop inter-professional interventional physical-, psychosocial-, educational- and support studies. In addition, the results could be incorporated into multidisciplinary follow-up care programs. To this end, functioning and health of children and adolescents with HCTD and their parents will be optimized. The knowledge about functioning and health derived from this thesis and the Follow You research program can also be transferred to multidisciplinary follow-up care programs and interventions for children and adolescents with other chronic diseases.

In addition, the collaboration of national and international networks, registries and websites should be strengthened to optimize awareness, knowledge, transparency and medical care for children and adolescents with HCTD. Moreover, national and international collaborations can facilitate future studies with larger patient groups with a rare disorder such as HCTD. Subsequently, new treatments and interventions can be developed to improve medical care and the functioning and health of every child and adolescent with HCTD worldwide.

To our knowledge there is no modified ICF-CY model available which can be used in pediatric clinical care. Therefore, I developed the new child and adolescent friendly model “Functioning and Health”, with the advice of colleagues, children, adolescents and parents. This new model is inspired by the ICF-CY and based on the knowledge from this thesis. The “Functioning and Health” model can be used by physicians, psychologists, social workers, allied health professionals and nurses to explore, explain, and discuss functioning and health and the interactions between domains together with children, adolescents and their parents. This will lead to awareness and understanding among children, adolescents and parents, and allows treatment options to be discussed. This model may also be useful in clinical care of children and adolescents with other chronic diseases.

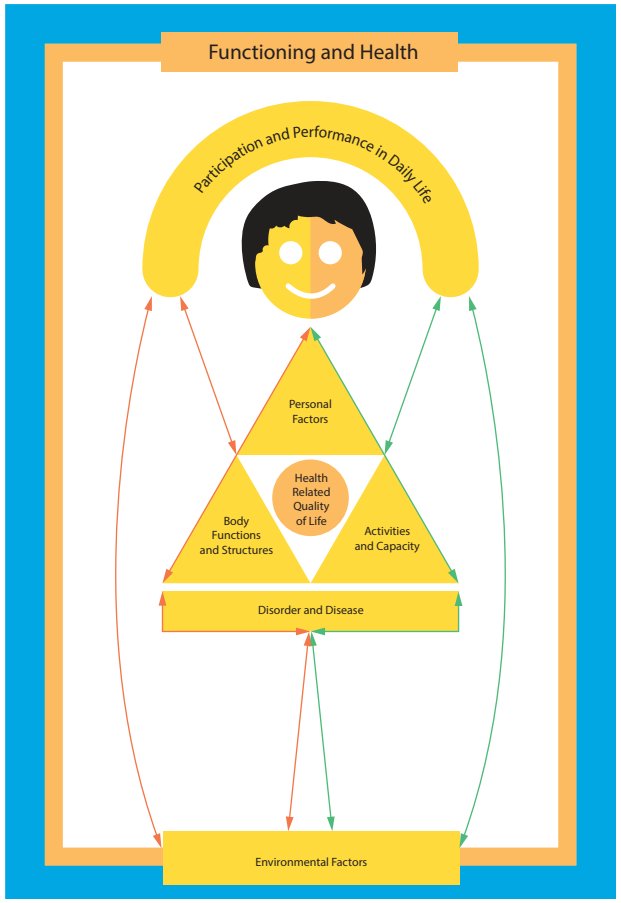


Figure 1. New child and adolescent friendly model "Functioning and Health". Green arrows indicate facilitating factors. Orange arrows indicate limiting factors. "Functioning" comprises all body functions, activities and participation; "Health" comprises complete physical, mental and social functioning; "Disorder and Disease" comprises physical and mental disorders and diseases; "Body Functions" are the physiological aspects of body systems; "Structures" are the anatomical support of the body; "Activity" is defined as the execution of a task or action; "Capacity" describes the person's ability to execute a task or an action; "Participation" refers to involvement in daily life; "Performance" describes what a person does in the environment; "Environmental Factors" are defined as the physical, social and attitudinal environment in which persons live and conduct their lives; "Personal Factors" comprise the particular background; "Health-Related quality of Life" is defined as the perceived (subjective) health related physical, mental, and social functioning. This new model is inspired by the International Classification of Functioning, Disability and Health for Children and Youth, developed by the World Health Organisation [11] and is based on the knowledge from the thesis "Functioning and Health of Children and Adolescents with Heritable Connective Tissue Disorders and their Parents" of Jessica Warnink-Kavelaars, Pediatric Rehabilitation Physician, Amsterdam UMC, location University of Amsterdam, Department of Rehabilitation Medicine, Amsterdam, The Netherlands . [1, 2, 64, 109]

CHAPTER 9

"Me, my friends and my school playground" by Lisanne Ipenburg (10 years)

Summary in Dutch

Samenvatting

Functioneren en gezondheid van kinderen en adolescenten met erfelijke bindweefsel aandoeningen en ouders

Erfelijke bindweefsel aandoeningen worden gekenmerkt door een pathologische bindweefsel afwijking (fragiliteit) in meerdere orgaansystemen. De fenotypes van de meest voorkomende erfelijke bindweefsel aandoeningen Marfan syndroom (MFS), Loeys-Dietz syndroom (LDS) en Ehlers-Danlos syndroom (EDS) laten vergelijkbare musculoskeletale, cardiovasculaire en cutane kenmerken zien die zich gedurende de kindertijd kunnen ontwikkelen. Bij aanvang van dit proefschrift was het onduidelijk hoe het gesteld is met functioneren en gezondheid van kinderen en adolescenten met erfelijke bindweefsel aandoeningen. Dit proefschrift heeft als doel de gevolgen van erfelijke bindweefsel aandoeningen op functioneren, gezondheid, gezondheidsgerelateerde kwaliteit van leven en mentale gezondheid van kinderen en adolescenten te onderzoeken.

Hoofdstuk 1 geeft een algemene inleiding over de meest voorkomende erfelijke bindweefsel aandoeningen en beschrijft de huidige literatuur over functioneren en gezondheid van kinderen en adolescenten met chronische ziekten, erfelijke bindweefsel aandoeningen en hun ouders.

Wereldwijd zijn in de afgelopen 30 jaar de prevalentie van chronische ziekten en beperkingen bij kinderen en adolescenten toegenomen. Chronische ziekten kunnen een negatieve invloed hebben op functioneren en gezondheid van kinderen. Er zijn ook enkele studies beschikbaar die de negatieve gevolgen van erfelijke bindweefsel aandoeningen bij kinderen beschrijven zoals pijn en vermoeidheid, beperkingen in activiteiten en verminderde deelname aan het dagelijks leven.

In Nederland is de medische zorg voor kinderen en adolescenten met erfelijke bindweefsel aandoeningen gecentreerd binnen de expertisecentra voor Marfan syndroom en aanverwante (bindweefsel) aandoeningen. In deze zorg is de betrokkenheid van een kinderrevalidatiearts, een multidisciplinair revalidatieteam en paramedici, werkzaam in de regio van het kind, van grote waarde. Deze expertisecentra zijn vertegenwoordigd binnen het "Nederlands Netwerk Marfan en aanverwante aandoeningen". In Europa zijn de expertisecentra vertegenwoordigd binnen de Europese Referentie Netwerken SKIN, VASCERN, en ReCONNET.

Verder wordt het door de Wereldgezondheidsorganisatie ontwikkelde model "Internationale Classificatie van Functioneren, Handicap en Gezondheid voor Kinderen en Jeugd" (ICF-CY), toegelicht.

Deel 1 Functioneren en gezondheid van kinderen en adolescenten met Marfan syndroom, ouders en gezin

Hoofdstuk 2 beschrijft de perspectieven van ouders ten aanzien van de gevolgen van MFS op het fysiek functioneren, activiteiten, participatie, externe en persoonlijke factoren van kinderen met MFS in de leeftijd van 4-12 jaar. Daarnaast beschrijft de studie de impact van het zorgen voor een kind met MFS op het leven van ouders en gezin.

Aan deze kwalitatieve studie namen 26 ouders deel aan individuele semigestructureerde interviews en drie focusgroepen. Voor de afnames van de interviews werd een nieuwe set van open vragen ontwikkeld, geïnspireerd op de ICF-CY. Audio-opnames werden getranscribeerd, gecodeerd en geanalyseerd met behulp van thematische analyse.

MFS-gerelateerde problemen werden gerapporteerd binnen alle ICF-CY domeinen. Geïdentificeerde thema's waren "problemen met het bijhouden van leeftijdsgenoten" en "fysiek anders zijn en anders voelen in vergelijking met leeftijdsgenoten". Ouders rapporteerden dat hun kind niet kon meekomen met leeftijdsgenoten vanwege lichamelijke problemen, pijn, vermoeidheid en beperkingen in activiteiten. Kinderen hadden moeite met onder andere lopen, rennen, fietsen, aan en uitkleden, gooien, schrijven en hanteren van bestek. Ook waren zij beperkt in school, sport, spel en andere vrijetijdsactiviteiten zoals feestjes, boswandelingen, pretpark bezoek en vakanties. Ouders vertelden ook dat hun kind zich anders voelde dan leeftijdsgenoten en aangaf er anders uit te zien door lichamelijke MFS-kenmerken zoals overmatige lengte groei, lange vingers, afwijkende stand van de borstkas, rug, knieën en voeten. Ouders rapporteerden dat kinderen en volwassenen soms vervelende en kwetsende opmerkingen maakten over het uiterlijk van hun kind en tijdens sporten en spelen.

Ouders gaven aan dat de grote zorgbehoefte en de zorgen over de ontwikkeling van hun kind met MFS, evenals het gebrek aan ondersteuning en een beperkt sociaal leven een grote impact hadden op het eigen dagelijkse leven.

Meerdere gezinsleden met MFS, complexe gezinsroosters en regelmatige aanpassingen van deze roosters wegens pijn, vermoeidheid of ziekte van een van de gezinsleden droegen bij aan een toegenomen gezinsbelasting. Gezinscohesie en zorgzaamheid voor elkaar werden als positief ervaren.

Concluderend ervaren ouders dat MFS gevolgen heeft voor functioneren en gezondheid van hun kinderen met MFS, het leven van ouders en het gezin. De nieuw ontwikkelde set open vragen geïnspireerd op de ICF-CY domeinen, kan van nut zijn tijdens consulten

en interviews met ouders om functioneren en gezondheid van hun jonge kinderen te exploreren.

Hoofdstuk 3 beschrijft de perspectieven van adolescenten ten aanzien van de gevolgen van MFS op lichamelijke functies, activiteiten, participatie, externe en persoonlijke factoren. Ook worden de ondersteuningsbehoeften van adolescenten in kaart gebracht.

Aan deze kwalitatieve studie namen 19 adolescenten met MFS in de leeftijd van 12 tot 18 jaar deel. Voor de afname van de interviews werd een nieuwe set van open vragen ontwikkeld, geïnspireerd op de ICF-CY. Audio-opnames werden getranscribeerd, gecodeerd en geanalyseerd met behulp van thematische analyse.

MFS-gerelateerde problemen werden gerapporteerd binnen alle ICF-CY domeinen. Geïdentificeerde thema's waren "problemen met het bijhouden van leeftijdsgenoten" en "fysiek anders zijn en zich anders voelen dan leeftijdsgenoten". In het ICF-CY model werden de door de adolescent benoemde MFS specifieke lichamelijke kenmerken, beperkingen in activiteiten en participatie en ondersteunende en belemmerende externe en persoonlijke factoren weergegeven. Adolescenten ervoeren problemen in het bijhouden van leeftijdsgenoten op school, sport, werk, vrije tijd, vriendschappen en relaties. Ze konden fysiek vaak niet voldoen aan de eisen die aan bijbaantjes en werk werden gesteld. Bovendien vonden adolescenten met MFS dat ze van leeftijdsgenoten verschilden door hun uiterlijke kenmerken passend bij MFS en beperkingen in activiteiten en participatie.

Omgevingsfactoren zoals "positieve steun van ouders, vrienden en docenten", "hulpmiddelen" en "aanpassingen in de omgeving" werden gerapporteerd als ondersteunende externe factoren voor sport, school, werk, vriendschappen en vrije tijd participatie; geen of negatieve steun werkte belemmerend.

Persoonlijke factoren zoals "positieve coping strategieën", een "gezonde levensstijl", "in staat zijn om hulp te vragen" en "goede planning" werden gerapporteerd als ondersteunende persoonlijke factoren voor sport, school, werk, vriendschappen en vrije tijd participatie. Daarentegen werden "het zich anders voelen" en een "laag gevoel van eigenwaarde" als belemmerende persoonlijke factoren ervaren.

Concluderend ervaren adolescenten dat het hebben van MFS gevolgen heeft voor het eigen functioneren en de gezondheid. De nieuw ontwikkelde set open vragen, geïnspireerd op de ICF-CY domeinen, kan van nut zijn tijdens consultaties en interviews met adolescenten om functioneren en gezondheid te exploreren.

Hoofdstuk 4 rapporteert de resultaten van het onderzoek naar de dagelijkse problemen en het psychosociale functioneren van ouders (met en zonder MFS) met een kind met MFS. Aan deze observationele cross-sectionele, studie deden 42 moeders (29% met MFS), en 25 vaders (60% met MFS) met een kind met MFS mee. De dagelijkse problemen en het psychosociale functioneren werden in kaart gebracht door afname van de gevalideerde screening-vragenlijst "de Last-thermometer voor ouders van een chronisch ziek kind". De resultaten werden vergeleken met een representatieve Nederlandse controlegroep van ouders met een gezond kind.

Er werden geen verschillen in percentages van klinisch relevante psychosociale problemen gerapporteerd tussen moeders en controlegroep-moeders; vaders en controlegroep-vaders en ook niet tussen de andere groepen. Er was geen significant verband tussen de psychosociale problemen van ouders en de systemische MFS-kenmerken van hun kind.

Concluderend vertonen ongeveer een derde van de ouders van een kind met MFS klinische relevante psychosociale problemen. Dit is vergelijkbaar met ouders van gezonde kinderen.

Deel 2 Functioneren en gezondheid van kinderen en adolescenten met erfelijke bindweefsel aandoeningen en hun ouders

Hoofdstuk 5 rapporteert de prevalentie en ernst van vermoeidheid, pijn, beperkingen in activiteiten en algemene gezondheid van kinderen en adolescenten met erfelijke bindweefsel aandoeningen. Dit is onderzocht met gestandaardiseerde gevalideerde vragenlijsten. In deze observationele, cross-sectionele, multicenter studie werden 107 kinderen, in de leeftijd van 4-18 jaar, met MFS, n = 62 (58%), LDS, n = 7 (7%), EDS, n = 9 (8%) en hEDS, n = 27 (27%) geïncludeerd. De PROMIS Vermoeidheid ouder-rapportage, de PROMIS Vermoeidheid kind-zelfrapportage, de pijn Visuele-Analoge-Schalen (VAS), de algemene gezondheid VAS en de "Childhood Health Assessment Questionnaire" (CHAQ) werden aangeboden.

De totale groep erfelijke bindweefsel aandoeningen liet significant hogere vermoeidheid, pijn, beperkingen in activiteiten en een lagere algemene gezondheid zien in vergelijking met de representatieve controlegroepen.

Exploratieve analyses van de MFS-, LDS-, EDS- en hEDS-subgroep lieten voor alle subgroepen significant hogere pijn, beperkingen in activiteiten en een lagere algemene

gezondheid zien in vergelijking met de representatieve controlegroepen. De hEDS- en de EDS-subgroep rapporteerden daarnaast ook een significant hogere ernstige vermoeidheid. Op alle vragenlijsten rapporteerde de hEDS-subgroep de meeste problemen en de MFS-subgroep de minste problemen.

De totale groep erfelijke bindweefsel aandoeningen liet significante verbanden zien tussen beperkingen in activiteiten en vermoeidheid, pijn en algemene gezondheid.

Concluderend is de totale groep van kinderen en adolescenten met erfelijke bindweefsel aandoeningen meer vermoeidheid, heeft meer pijn, is beperkter in activiteiten en heeft een verminderde algemene gezondheid ten opzichte van leeftijdsgenoten. Op de vragenlijsten rapporteerde de hEDS-subgroep de meeste problemen en de MFS-subgroep de minste problemen.

Onze resultaten pleiten voor het systematisch monitoren van pijn, vermoeidheid, activiteiten en algemene gezondheid van kinderen en adolescenten met erfelijke bindweefsel aandoeningen met gestandaardiseerde gevalideerde vragenlijsten. De uitkomsten kunnen dan besproken worden tijdens de afspraak in het ziekenhuis.

Hoofdstuk 6 onderzoekt gezondheidsgerelateerde kwaliteit van leven en mentale gezondheid van kinderen en adolescenten met erfelijke bindweefsel aandoeningen met behulp van gestandaardiseerde gevalideerde vragenlijsten.

In deze observationele cross-sectionele, multicenter studie werden 126 kinderen, in de leeftijd van 4-18 jaar, met MFS, n = 74 (59%), LDS, n = 8 (6%), EDS, n = 15 (12%), hEDS, n = 29 (23%) geïncludeerd. De Child Health Questionnaires" (CHQ-PF50) en de "Strengths and Difficulties Questionnaire (SDQ) werden aangeboden aan alle ouders. De CHQ-CF45 werd aangeboden aan kinderen vanaf 8 jaar.

De door ouders gerapporteerde gezondheidsgerelateerde kwaliteit van leven van de totale groep erfelijke bindweefsel aandoeningen liet significant lagere scores zien voor de fysieke en de psychosociale gezondheidsgerelateerde kwaliteit van leven in vergelijking met een representatieve controlegroep. Dit duidt op een verminderde totale gezondheid gerelateerde kwaliteit van leven. Kinderen en adolescenten rapporteerden vergelijkbare resultaten. In de sub-analyses rapporteerden de hEDS-subgroep en de MFS-subgroep beide een verminderde gezondheid gerelateerde kwaliteit van leven.

De door de ouders gerapporteerde mentale gezondheid van de totale groep erfelijke bindweefsel aandoeningen toonde significant verhoogde scores voor "Totale Moeilijkheden". Dit wijst op een verminderde mentale gezondheid. In de sub-analyses

rapporteerden de hEDS-subgroep een verminderde mentale gezondheid en de MFS-subgroup een normale mentale gezondheid.

Concluderend heeft de totale groep van kinderen en adolescenten met erfelijke bindweefsel aandoeningen een verminderde gezondheidsgerelateerde kwaliteit van leven en verminderde mentale gezondheid. Op beide vragenlijsten rapporteerde de hEDS-subgroep de meeste problemen en de MFS-subgroep de minste problemen.

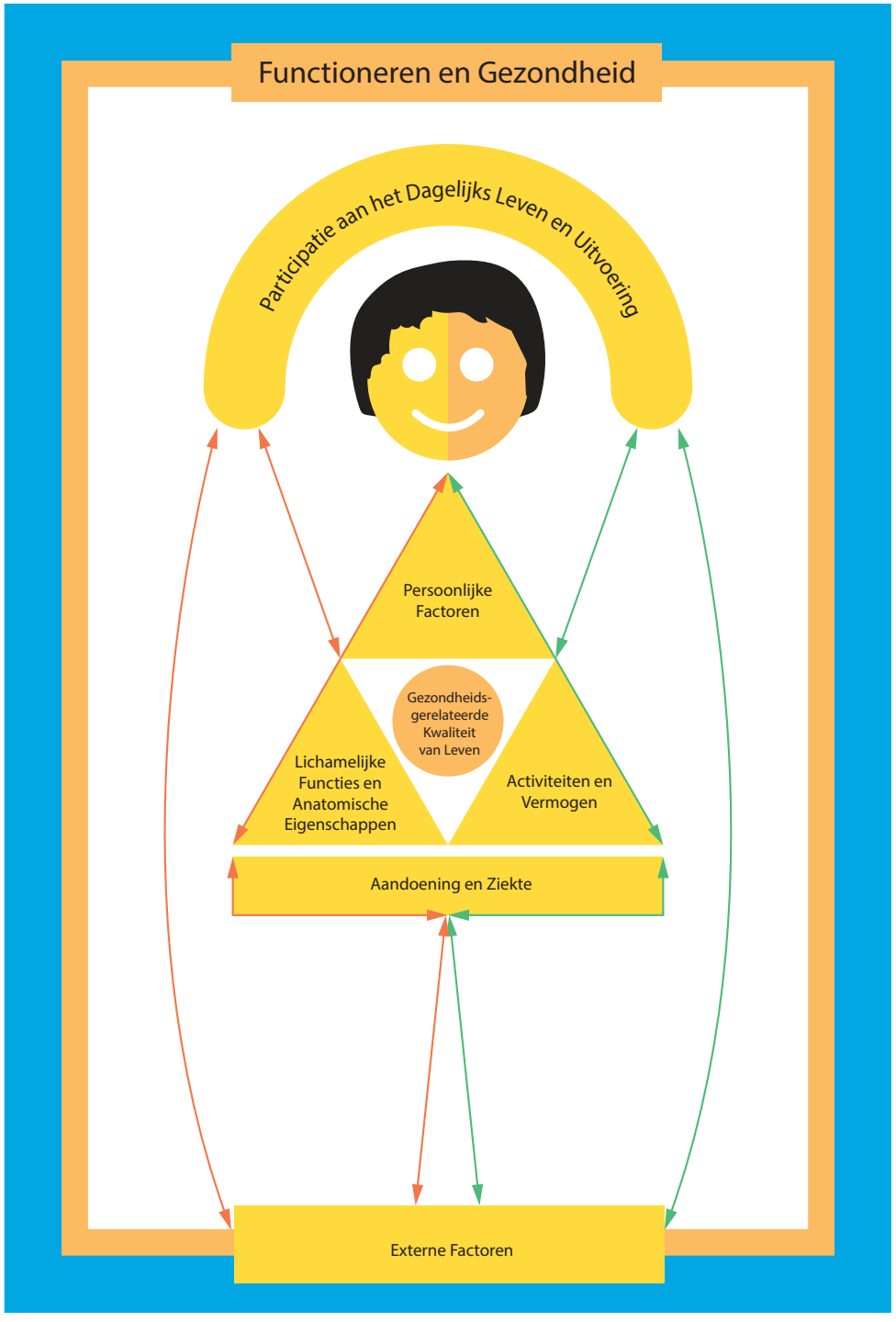
Onze resultaten pleiten voor het systematisch monitoren van gezondheidsgerelateerde kwaliteit van leven en de mentale gezondheid van kinderen en adolescenten met erfelijke bindweefsel aandoeningen met gestandaardiseerde gevalideerde vragenlijsten. De uitkomsten kunnen dan besproken worden tijdens de afspraak in het ziekenhuis.

Hoofdstuk 7 presenteert de algemene conclusies van de afzonderlijke studies in dit proefschrift en bespreekt de belangrijkste bevindingen in een breder perspectief met betrekking tot de klinische relevantie, methodologische overwegingen, implicaties voor de medische zorg en toekomstig onderzoek.

Dit proefschrift laat zien dat functioneren en gezondheid van kinderen en adolescenten met erfelijke bindweefsel aandoeningen is verminderd in vergelijking met representatieve controlegroepen. Daarnaast geeft dit proefschrift inzicht in de interacties tussen domeinen en ondersteunende en belemmerende externe- en persoonlijke factoren. De meeste problemen worden gerapporteerd door kinderen en adolescenten met hEDS en de minste bij MFS.

De resultaten van dit proefschrift pleiten voor systematische monitoring met gestandaardiseerde gevalideerde vragenlijsten met betrekking tot functioneren en gezondheid van kinderen en adolescenten met erfelijke bindweefsel aandoeningen. Bij voorkeur vindt monitoring plaats binnen een multidisciplinair follow-up zorgprogramma. De nieuwe kennis over functioneren en gezondheid van dit proefschrift kan ook worden overgedragen naar multidisciplinaire follow-up zorgprogramma's voor kinderen en adolescenten met andere chronische ziekten.

De huidige medische zorg voor kinderen en adolescenten met bindweefsel aandoeningen heeft baat bij een (toekomstige) "erfelijke bindweefsel aandoeningen" - specifieke set van fysieke metingen. Hiermee kunnen lichamelijke karakteristieken, activiteiten en fysiek vermogen in kaart worden gebracht door objectieve metingen. Met deze data kunnen "erfelijke bindweefsel aandoeningen" - normatieve gegevens gegenereerd worden. Ook zal het bijdragen aan de bewustwording en kennis over



Uitleg figuur: het nieuwe kind- en adolescent vriendelijke, model "Functioneren en Gezondheid". Groene pijlen geven ondersteunende factoren aan. Oranje pijlen geven belemmerende factoren aan. "Functioneren" bevat alle lichamelijke functies en anatomische eigenschappen, activiteiten en participatie; "Gezondheid" bevat het complete fysieke, mentale en sociale functioneren; "Aandoening en Ziekte" geven de fysieke en mentale aandoeningen en ziektes weer; "Lichamelijke Functies" zijn fysiologische en mentale eigenschappen van het lichaam; "Anatomische Eigenschappen" betreffen de positie, aanwezigheid, vorm en continuïteit van onderdelen van het lichaam; "Activiteiten" zijn onderdelen van het handelen van een persoon. "Vermogen" classificeert of een persoon een taak of activiteit wel of niet kan uitvoeren; "Participatie" is iemands deelname aan het maatschappelijk leven; "Uitvoering" classificeert wat iemand in de eigen omgeving doet; "Externe Factoren" vormen de fysieke en sociale omgeving waarin personen leven; "Persoonlijke Factoren" vormen de specifieke achtergrond; "Gezondheidgerelateerde Kwaliteit van Leven" wordt gedefinieerd als het waargenomen (subjectieve) gezondheidsgerelateerde fysieke, mentale en sociale functioneren. Het model is geïnspireerd op de Internationale Classificatie van Functioneren, Handicap en Gezondheid voor Kinderen en Jeugd en op het proefschrift "Functioneren en gezondheid van kinderen en adolescenten met erfelijke bindweefsel aandoeningen en ouders: van Jessica Warnink-Kavelaars, Kinderrevalidatiearts, Amsterdam UMC, locatie Universiteit van Amsterdam, Afdeling Revalidatiegeneeskunde, Amsterdam, Nederland

functioneren en gezondheid, klinisch redeneren en risicoprofilering van kinderen en adolescenten met erfelijke bindweefsel aandoeningen.

Studies naar het effect van interventies ter verbetering van functioneren en gezondheid bij kinderen en adolescenten met erfelijke bindweefsel aandoeningen zijn zeer schaars. Het Follow You onderzoeksprogramma zal in de komende jaren nieuwe resultaten publiceren over een interprofessionele, fysieke, psychosociale en educatieve interventie. Dit draagt bij aan de ontwikkeling van nieuwe interprofessionele fysieke-, psychosociale-, educatieve- en ondersteunende interventie studies.

Nederlandse (Nederlands Netwerk Marfan en aanverwante aandoeningen), Europese (European Reference Network (ERN) Skin, ERN VASCERN, ERN ReCONNET) en wereldwijde samenwerking evenals de ontwikkeling van websites en registraties zijn nodig om het bewustzijn, de kennis, de transparantie en de medische zorg voor kinderen en adolescenten met erfelijke bindweefsel aandoeningen te versterken. Door internationale studies met grotere groepen kinderen en adolescenten kunnen nieuwe behandelingen en interventies worden ontwikkeld ten behoeve van het optimaliseren van functioneren en gezondheid van kinderen en adolescenten met erfelijke bindweefsel aandoeningen wereldwijd.

Voor zover bekend is er geen aangepast ICF-CY model beschikbaar dat gebruikt wordt in de medische zorg voor kinderen en adolescenten. Daarom heb ik, samen met adviezen van kinderen, adolescenten, ouders en collega's, het nieuwe kind en adolescent vriendelijke model "Functioneren en Gezondheid" ontwikkeld. Dit nieuwe model is geïnspireerd op de ICF-CY en gebaseerd op de kennis uit dit proefschrift. Dit

"Functioneren en Gezondheid" model kan gebruikt worden door artsen, psychologen, maatschappelijk werkers, paramedici en verpleegkundigen om gezamenlijk met kinderen en ouders functioneren, gezondheid en de interacties tussen domeinen te exploreren en te bespreken. Dit zal leiden tot grotere bewustwording en begrip en maakt het mogelijk om samen met kinderen en ouders behandelopties in kaart te brengen. Dit model kan ook nuttig zijn in de medische zorg voor kinderen en adolescenten met andere chronische ziekten.

Authors' contributions per chapter

Chapter 2

Marfan syndrome in childhood: Parents' perspectives of the impact on daily functioning of children, parents and family; a qualitative study.

Warnink-Kavelaars J, Beelen A, Dekker S, Nollet F, Menke LA, Engelbert RHH.
BMC Pediatr. 2019;19(1):262. Published 2019 Jul 29. doi:10.1186/s12887-019-1612-6

JW-K participated in the study design, data collection, analysis, interpretation and the writing of the report. AB participated in the study design, the data analysis and interpretation. LM and SD participated in data collection, analysis and the interpretation of the data. RE and FN participated in the interpretation of the data. All authors revised this article critically and approved the final manuscript.

Chapter 3

Marfan syndrome in adolescence: Adolescents' perspectives on (physical) functioning, disability, contextual factors and support needs.

Warnink-Kavelaars J, Beelen A, Goedhart T, de Koning LE, Nollet F, Alsem MW, Menke LA, Engelbert RHH. *Eur J Pediatr*. 2019;178(12):1883-1892. doi:10.1007/s00431-019-03469-7

JW-K participated in the study design, data collection, analysis and interpretation, and the writing of the report. AB participated in the study design, the data analysis and interpretation. TG participated in data analysis and interpretation. LM, MA, RE and FN participated in the interpretation of the data. All authors revised this article critically and approved the final manuscript.

Chapter 4

Parenting a child with Marfan syndrome: Distress and everyday problems.

Warnink-Kavelaars J, van Oers HA, Haverman L, Buizer AI, Alsem MA, Engelbert RHH, Menke LA. *Am J Med Genet A*. 2021;185(1):50-59. doi:10.1002/ajmg.a.61906

JW-K participated in the study design, data collection, analysis and interpretation, and the writing of the report. HO and LM participated in the study design, data collection and analysis and interpretation. All authors revised this article critically and approved the final manuscript.

Chapter 5

Heritable Connective Tissue Disorders in childhood: Fatigue, pain, disability and general health.

Warnink-Kavelaars J, de Koning LE, Rombaut L, Alsem MW, Menke LA, Oosterlaan J, Buizer AI, Engelbert RHH on behalf of the Pediatric Heritable Connective Tissue Disorders Study Group*. *Genes (Basel)*. 2021;12(6):831. Published 2021 May 28. doi:10.3390/genes12060831

JW-K participated in the study design, data collection, analysis and interpretation, and the writing of the report. LK participated in the study design, data collection, analysis and interpretation. LR, MA, LM, JO, AB and RE participated in the study design, analysis and interpretation. All authors revised this article critically, approved the final manuscript and agreed to its submission for publication. J W-K, LM and RE had complete access to the study data that supported the publication. The members of the Pediatric Heritable Connective Tissue Disorders Study Group: Baars MJH, de Boer R, Braam K, Dulfer E, Hilhorst-Hofstee Y, van der Hulst AE, Kempers MJE, Krapels IPC, Loeys BL, van der Looven R, Malfait F, Muino Mosquera L, van Rossum MAJ, Stoelinga F delivered a substantial contribution to the acquisition of data and reviewed and approved the final manuscript.

Chapter 6

Heritable Connective Tissue Disorders in childhood: Decreased health-related quality of life and mental health.

Warnink-Kavelaars J, de Koning LE, Rombaut L, Alsem MW, Menke LA, Buizer AI, Engelbert RHH, Oosterlaan J on behalf of the Pediatric Heritable Connective Tissue Disorders Study Group*. [published online ahead of print, 2022 Apr 8]. *Am J Med Genet A*. 2022;10.1002/ajmg.a.62750. doi:10.1002/ajmg.a.62750

JW-K participated in the study design, data collection, analysis and interpretation, and the writing of the report. LK participated in the study design, data collection, analysis and interpretation. LR, MA, LM, AB RE and JO participated in the study design, analysis and interpretation. All authors revised this article critically and approved the final manuscript
*The members of the Pediatric Heritable Connective Tissue Disorders Study Group: Baars MJH, de Boer R, Braam K, Dulfer E, Hilhorst-Hofstee Y, van der Hulst AE, Kempers MJE, Krapels IPC, Loeys BL, van der Looven R, Malfait F, Muino Mosquera L, van Rossum MAJ, Stoelinga F delivered a substantial contribution to the acquisition of data and reviewed and approved the final manuscript.

"Me and my friends at school" by Lily-Anne (9 years)

List of abbreviations

CHAQ	Childhood Heath Assessment Questionnaire
CHQ	Child Health Questionnaire
DT-P	Distress Thermometer for Parents of a chronically ill child
ECTS	European Credit Transfer and Accumulation System
EDS	Ehlers-Danlos syndromes
ERN	European Reference Network
HCTD	Heritable Connective Tissue Disorders
hEDS	hypermobile Ehlers-Danlos syndrome
HRQoL	Health-Related Quality of Life
HSD	Hypermobile Spectrum Disorder
ICF-CY	International Classification of Functioning, Disability and Health for Children and Youth
LDS	Loeys-Dietz syndrome
MFS	Marfan syndrome
MCID	Minimal Clinically Important Differences
PROMIS	Patient Reported Outcomes Measurement Information System
SDQ	Strength and Difficulties Questionnaire
UMC	University Medical Center
US	United States
VAS	Visual Analogue Scale
WHO	World Health Organization

PhD Portfolio

Amsterdam UMC Doctoral School PhD Portfolio
Summary of PhD training, teaching and parameters of esteem

Name: Jessica Warnink-Kavelaars
PhD period: January 2017 – February 2022
Promotor: prof. dr. R.H.H. Engelbert
Promotor: (2019 - 2022): prof. dr. A.I. Buizer
Promotor: (2017 - 2019): prof. dr. F. Nollet
Co-promotor: dr. L.A. Menke
Co-promotor: (2018-2022): dr. M.W. Alsem
Co-promotor: (2017-2018): dr. J.A. Beelen
Department: Rehabilitation Medicine, Amsterdam UMC

I. PhD TRAINING

	Year	Workload (ECTS*)
Courses Amsterdam UMC Doctoral School		
E-BROK Basic Course Legislation and Organization for Clinical Researchers	2017	1.5
Endnote	2017	0.1
Qualitative Health Research	2017	1.9
Scientific writing in English	2018	1.5
Practical Biostatistics	2019	1.4
Observational Epidemiology	2019	0.6
Research Data management	2020	0.2
Continues eBROK	2021	1
Advanced topics in Biostatistics	2021	2.1
	Total	**10.3**
Specific courses		
Pediatric Rehabilitation 2017	2017	0.9
Gait and exercise	2017	0.8
Developmental Appreciative Navigational Approach (DANA) to IFMS (Individual Functioning of Medical Specialists) - coaching	2018	0.6
Strategic leadership for physicians	2018	2.1
Pediatric Rehabilitation 2018	2018	0.9
Teach the teacher 2018	2018	0.4
POBOT Post graduate training spasticity and ultrasound upper extremity; advanced course	2019	0.6
Pediatric Rehabilitation 2019	2019	0.9
Teach the teacher 2019	2019	0.4
Pediatric Rehabilitation 2021 (webinar)	2021	0.3
Pediatric exercise	2021	0.3
	Total	**8.2**
Seminars, workshops and master classes		
Weekly educational and research meetings; department of rehabilitation, Amsterdam UMC, Amsterdam, the Netherlands	2017-2022	5.0
	Total	**5.0**
Oral presentations		
Marfan syndrome in childhood; Qualitative research; research meeting, department of rehabilitation Amsterdam UMC, the Netherlands	2017	0.5
Marfan syndrome in childhood: Parents' perspectives of the impact on daily functioning of children, parents and family; a qualitative study. Marfan European Network, Oestgeest, the Netherlands	2017	0.5
Shared decision making in in care for rare disorders. Keynote speaker. Conference Marfan patient association, Soesterberg, the Netherlands	2018	0.5
Marfan syndrome in childhood: Parents' perspectives of the impact on daily functioning of children, parents and family; a qualitative study. The 10th International Research Symposium on Marfan Syndrome and related disorders, Hilton, Amsterdam, the Netherlands	2018	0.5
Marfan syndrome in adolescence: Adolescents' perspectives on (physical) functioning, disability, contextual factors and support needs. Hereditary and Congenital Disorders Symposium, Amsterdam, the Netherlands	2018	0.5
Marfan syndrome in adolescence: Adolescents' perspectives on (physical) functioning, disability, contextual factors and support needs. European Academy of Childhood Disability Conference, Paris, France	2019	0.5
Collaboration and future of the Dutch expert network Marfan and related disorders. 1ste Conference of the Dutch expert network Marfan and related disorders, Amsterdam, the Netherlands	2019	0.5
Marfan syndrome in adolescence: Adolescents' perspectives on (physical) functioning, disability, contextual factors and support needs. Dutch Congress of Rehabilitation Medicine, Utrecht, the Netherlands	2019	0.5

Physical and psychosocial functioning in children and adolescents with Connective Tissue Disorders; lessons learned and future directives. Keynote speaker. Conference European Reference Network Skin, Gent, Belgium	2019	0.5
Pediatric Marfan syndrome: clinical care and research. Regional research meeting, Amsterdam, the Netherlands	2020	0.5
Follow Me; results after 2 years. Follow Me research meeting, Amsterdam, the Netherlands	2020	0.5
Heritable Connective Tissue Disorders in childhood: Fatigue, pain, disability and general health. Keynote speaker. Conference European Reference Network SKIN, scientific day, international webinar	2021	0.5
Heritable Connective Tissue Disorders in childhood: Fatigue, pain, disability and general health. European Academy of Childhood Disability Conference, international webinar	2021	0.5
Heritable Connective Tissue Disorders in childhood: Decreased health-related quality of life and mental health. Conference of the Dutch expert network Marfan and related disorders, Maastricht, the Netherlands	2022	0.5
	Total	**7.0**

Poster presentations		
Marfan syndrome in childhood: Parents' perspectives of the impact on daily functioning of children, parents and family; a qualitative study. The International Symposium of the Ehlers-Danlos Syndromes, Ghent, Belgium	2018	0.5
Marfan syndrome in childhood: Parents' perspectives of the impact on daily functioning of children, parents and family; a qualitative study. Dutch Congress of Rehabilitation Medicine, Groningen, the Netherlands	2018	0.5
Marfan syndrome in childhood: Parents' perspectives of the impact on daily functioning of children, parents and family; a qualitative study. 3rd Amsterdam Movements Science Annual research meeting, Amsterdam, the Netherlands	2019	0.5
Marfan syndrome in childhood: Parents perspectives of the impact on children, parents and family. European Academy of Childhood Disability Conference, Paris, France	2019	0.5
Parenting a child with Marfan syndrome: Distress and everyday problems. Dutch Congress of Rehabilitation Medicine, webinar	2020	0.5
Heritable Connective Tissue Disorders in childhood: Decreased health-related quality of life and mental health. European Academy of Childhood Disability Conference, Barcelona, Spain	2022	0.5
	Total	**3.0**

(Inter)national conferences		
International symposium on surgery of the spastic upper limb, Paris, France	2017	0.5
European Academy of Childhood Disability Conference, Amsterdam, the Netherlands	2017	1.0
Marfan European Network, Oestgeest, the Netherlands	2017	0.25
The 10th International Research Symposium on Marfan syndrome and related disorders Hilton, Amsterdam, the Netherlands	2018	0.75
The International Symposium of the Ehlers-Danlos Syndromes, Ghent, Belgium	2018	0.75
Hereditary and Congenital Disorders Symposium, Amsterdam, the Netherlands	2018	0.25
Dutch Congress of Rehabilitation Medicine, Groningen, the Netherlands	2018	0.5
3rd Amsterdam Movements Science Annual research meeting, Amsterdam, the Netherlands	2019	0.25
European Academy of Childhood Disability Conference, Paris, France	2019	1
1ste Conference of the Dutch expert network Marfan and related disorders, Amsterdam, the Netherlands	2019	0.25
Dutch Congress of Rehabilitation Medicine, Utrecht, the Netherlands	2019	0.5
Conference European Reference Network Skin, Gent, Belgium	2019	0.75
Dutch Congress of Rehabilitation Medicine, international webinar	2020	0.25
Conference European Reference Network Skin, scientific day, international webinar	2021	0.25
European Academy of Childhood Disability Conference, international webinar	2021	1.0
International symposium on surgery of the spastic upper limb, international webinar	2021	0.25
2th Conference of the Dutch expert network Marfan and related disorders, Maastricht, the Netherlands	2022	0.25
International symposium on surgery of the spastic upper limb, Amsterdam, the Netherlands	2022	0.75
European Academy of Childhood Disability Conference, Barcelona, Spain	2022	1
	Total	**10.5**

II. TEACHING

	Year	Workload (ECTS*)
Lecturing		
Pediatric Marfan: physical functioning and the impact of Marfan on daily life. Elective educational program medical school Amsterdam UMC	2018-2019	0.5
Transition and the ICF-CY model. Elective educational program medical school Amsterdam UMC	2015-2019	0.75
Inter-professional education; collaboration of the educational program of the medical school Amsterdam UMC and Center of Expertise Urban Vitality, Amsterdam University of Applied Sciences	2019	1.5
Physical examination. Educational program medical school Amsterdam UMC	2016-2019	0.75
	Total	**3.5**
Tutoring		
Tutoring residents rehabilitation medicine. Pediatric Marfan syndrome: physical functioning and the impact on daily life	2017-2019	0.9
Tutoring: physical examination and skills	2017- 2019	1
	Total	**1.9**
Supervising research		
Supervision of Sarah Dekker, resident rehabilitation medicine. Research project: Self-worth and self-competence in children and adolescents aged 8 to 18 years with Marfan syndrome	2017-2019	5.0
Supervision of Tine Goedhart; medical student; 4 month research internship	2019	1.5
Supervision of Kobie Verhoogt; medical student; 4 month research internship	2020	1.5
	Total	**8.0**
ECTS PhD period 2017-2022	**Total**	**57.4**

III. Parameters of Esteem

	Year
Grants	
SIA RAAK-PRO, part of the Dutch Organization for Scientific Research, project number NWO; SVB.RAAK>PRO02.007 allocated to "Follow You – a follow up program on physical, psychosocial functioning and participation in children and adolescents with (Heritable) Connective Tissue Disorders". Applicants: prof. dr. R.H.H. Engelbert, J. Warnink-Kavelaars and L. Rombaut	2017
ZonMw/VSOP, project number 2016124303 allocated to "Shared decision making, rare disorders". Applicants: Marfan patient association and J. Warnink-Kavelaars	2018
ZonMw /VSOP, project number 742006010 allocated to "Working together to provide the best care - From intent to implementation. Applicants: Marfan patient association and J. Warnink-Kavelaars	2020
Dutch patient associations/VSOP project number JZ05 allocated to KIDZ-project "Right care in the right place - Expertise Connected" to develop the national MFS website (https://Marfan-expertise.net). Applicants: Dutch Network Marfan and related disorders (chair J. Warnink-Kavelaars)	2021
Awards	
Nomination for best plenary poster PITCH presentation. Marfan syndrome in childhood: Parents' perspectives of the impact on daily functioning of children, parents and family; a qualitative study. Dutch Congress of Rehabilitation Medicine, Groningen, the Netherlands	2018
European Academy of Childhood Disability 2021: EACD Early Career Researcher Award- 2nd place out of 70 nominated researchers from 54 countries	2021
European Reference Networks	
ERN SKIN	2019-
ERN VASCERN	2017-
ERN eUROGEN	2021-
Expert centers	
Amsterdam UMC expert center of Marfan syndrome and related disorders	2017-
Amsterdam UMC expert center Cerebral Palsy	2017-
Amsterdam UMC expert center Anorectal Malformations	2019-
Networks	
Dutch Expert Network Cerebral Palsy	2015-
Dutch Expert Network Marfan and related disorders (co-founder; chair)	2019-

Associations	
Netherlands Society of Rehabilitation Medicine (VRA)	2011-
VRA Pediatric Rehabilitation section (Kindersectie)	2011-

*ECTS: European Credit Transfer and Accumulation System. For its courses, the Amsterdam UMC Doctoral School adheres to the ECTS system: workload of 28 hours = 1 ECTS. There is no formal requirement for a minimum number of courses, hours or ECTS points for AMC PhD candidates. The Amsterdam UMC Doctoral School recommends 20-30 ECTS points for PhD training and teaching during the four-year fulltime PhD project.

List of publications

This thesis

Warnink-Kavelaars J, Beelen A, Dekker S, Nollet F, Menke LA, Engelbert RHH.
Marfan syndrome in childhood: parents' perspectives of the impact on daily functioning of children, parents and family; a qualitative study. *BMC Pediatr*. 2019;19(1):262. Published 2019 Jul 29. doi:10.1186/s12887-019-1612-6

Warnink-Kavelaars J, Beelen A, Goedhart T, de Koning LE, Nollet F, Alsem MW, Menke LA, Engelbert RHH. Marfan syndrome in adolescence: adolescents' perspectives on (physical) functioning, disability, contextual factors and support needs. *Eur J Pediatr*. 2019;178(12):1883-1892. doi:10.1007/s00431-019-03469-7

Warnink-Kavelaars J, van Oers HA, Haverman L, Buizer AI, Alsem MW, Engelbert RHH, Menke LA (2021). Parenting a child with Marfan syndrome: Distress and everyday problems. *Am J Med Genet A*. 2021;185(1):50-59. doi:10.1002/ajmg.a.61906

Warnink-Kavelaars J, de Koning LE, Rombaut L, Alsem MW, Menke LA, Oosterlaan J, Buizer AI, Engelbert RHH on behalf of the Pediatric Heritable Connective Tissue Disorders Study Group* (2021). Heritable Connective Tissue Disorders in Childhood: Increased Fatigue, Pain, Disability and Decreased General Health. *Genes (Basel)*. 2021;12(6):831. Published 2021 May 28. doi:10.3390/genes12060831

Warnink-Kavelaars J, de Koning LE, Rombaut L, Alsem MW, Menke LA, Buizer AI, Engelbert RHH, Oosterlaan J on behalf of the Pediatric Heritable Connective Tissue Disorders Study Group*. Heritable Connective Tissue Disorders in childhood: Decreased health-related quality of life and mental health. [published online ahead of print, 2022 Apr 8]. *Am J Med Genet A*. 2022;10.1002/ajmg.a.62750. doi:10.1002/ajmg.a.62750

Other international peer-reviewed publications

Louwers A, **Warnink-Kavelaars J**, Daams J, Beelen A.
Effects of upper extremity surgery on activities and participation of children with cerebral palsy: a systematic review. *Dev Med Child Neurol*. 2020;62(1):21-27. doi:10.1111/dmcn.14315

Louwers A, **Warnink-Kavelaars J**, Obdeijn M, Kreulen M, Nollet F, Beelen A.
Effects of Upper-Extremity Surgery on Manual Performance of Children and Adolescents with Cerebral Palsy: A Multidisciplinary Approach Using Shared Decision-Making. *J Bone Joint Surg Am*. 2018;100(16):1416-1422. doi:10.2106/JBJS.17.01382

Warnink-Kavelaars J, Vermeulen RJ, Buizer AI, Becher JG.
Botulinum neurotoxin treatment in children with cerebral palsy: validation of a needle placement protocol using passive muscle stretching and relaxing. *Dev Med Child Neurol*. 2016;58(12):1281-1287. doi:10.1111/dmcn.13176

Warnink-Kavelaars J, Vermeulen RJ, Becher JG.
Study protocol: precision of a protocol for manual intramuscular needle placement checked by passive stretching and relaxing of the target muscle in the lower extremity during BTX-A treatment in children with spastic cerebral palsy, as verified by means of electrical stimulation. *BMC Pediatr*. 2013;13:129. Published 2013 Aug 22. doi:10.1186/1471243113-129

Kavelaars J, Tamsma JT, Meinders AE.
Hypernatremia in a non insulin dependent (type 2) diabetic patient with central diabetes insipidus. *Neth J Med*. 2001;58(3):150-154. doi:10.1016/s0300-2977(01)00083-3

Young LR, Hecht H, Lyne LE, Sienko KH, Cheung CC, **Kavelaars J**.
Artificial gravity: head movements during short-radius centrifugation. *Acta Astronaut*. 2001;49(3-10):215-226. doi:10.1016/s0094-5765(01)00100-x

Hecht H, **Kavelaars J**, Cheung CC, Young LR.
Orientation illusions and heart-rate changes during short-radius centrifugation. *J Vestib Res*. 2001;11(2):115-127. PMID 11847455

Kingma H, **Kavelaars J**, van Tienen N, Caris R (2001).
Evaluation of the statolith function by measurement of ocular counterrolling? *Oto-Rhino-Laryngologia Nova*, *11*(2), 68-79. doi:10.1159/000048743

Publications in Dutch

Warnink-Kavelaars J, Baars M, Hilhorst-Hofstee Y, Kempers M, Dulfer E, Krapels I, Rosenbrand N (2020).
Netwerken in de zorg voor zeldzaam: Nederlands Netwerk Marfan. *Nederlands Tijdschrift voor Revalidatiegeneeskunde*, 1, 28-30.

Louwers A, **Warnink-Kavelaars J**, Obdeijn M, Kreulen M, Nollet F, Beelen A (2019).
Handchirurgie bij cerebrale parese. *Tijdschrift voor handtherapie*. April 2019, 4-9

Louwers A, van der Molen-Meulmeester L, van der Horst C, **Warnink-Kavelaars J** (2019).
Effectief gebruik van de "kleine" hand: van fixatie tot greep. *Tijdschrift voor handtherapie.* April 2019, 32-35

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PhD team

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Leden van de promotiecommissie

Prof. dr. J.B. van Goudoever (AMC-UvA), prof. dr. N.A. Blom (AMC-UvA), prof. dr. R.C.M. Hennekam (AMC-UvA), prof. dr. A.M.C.F. Verbunt (Universiteit Maastricht), prof. dr. E.A.A. Rameckers (Universiteit Hasselt) en prof. dr. J.W. Gorter (Universiteit Utrecht en Canchild) hartelijk dank voor de bereidheid mijn proefschrift kritisch te lezen en zitting te nemen in de promotiecommissie.

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Nederlands Netwerk Marfan en aanverwante aandoeningen

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Familie en schoonfamilie

Familie en schoonfamilie, bedankt voor de felicitaties na elke publicatie. Dat gaf weer energie voor een volgend artikel.

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Wat een feest dat ik jullie allemaal zo dicht in mijn buurt heb!

Gezin
Mijn eigen gezin, de mooiste en belangrijkste personen uit mijn leven, Tjebbe, Daan, Annebel en Rosa. Jullie zorgen elke dag voor geluk in mijn leven en meer. Wat ben ik trots op jullie allemaal: de onvoorwaardelijke liefde, de steun, de grappen en de humor, de zelfstandige beslissingen en de prachtige sterke familieband. Ik kan niet zonder jullie.

Mijn drie kinderen
Daan, mijn prachtige lieve zoon. Ik geniet van je relaxte houding, je opgewekte karakter, je mooie verhalen, je positieve kijk op de wereld en je humor.

Annebel, mijn prachtige lieve dochter. Ik geniet van je lieve en levenslustige karakter, zorgzaam en tegelijkertijd zo stoer, je positieve uitstraling, je surfen en sporten, je humor en je zonnige kijk op het leven.

Rosa, mijn prachtige lieve dochter. Ik geniet van je open houding, je vrolijke karakter, je stralende lach, je grapjes, je enthousiasme en je altijd positieve energie.

Jullie zijn alle drie heel bijzonder en maken de wereld mooier.

Tjebbe
Tjebbe, mijn prachtige lieve man. In 1995 zag ik je zitten op een barkruk in een kroeg in Maastricht. Je keek voetbal. Geen wetenschap of onderbouwing, nee, ik wist het gewoon zeker, ik voelde het: dit is de liefde van mijn leven.

Lieve Tjebbe, bedankt voor het geluk dat je mij geeft, ons leven dat we samen opgebouwd hebben, de onvoorwaardelijke liefde die ik elke dag voel voor jou en van jou, je altijd en eeuwige steun voor van alles en nog wat, je positieve karakter, je vrolijke lach en voor onze prachtige kinderen die we samen opvoeden.

Weet je nog, het liedje van onze trouwerij?

We dansen, dansen de wereld rond,
We dansen, dansen samen,
Aan jou wil ik mijn hart geven,
Met jou wil ik mijn leven leven.

Allerliefste Tjebbe, Daan, Annebel en Rosa; ik houd van jullie van Zandvoort naar de maan, rondje door het heelal, nog een rondje en nog een rondje, oneindig veel.

About the author

Jessica Warnink-Kavelaars was born on 26 September, 1975 in Eindhoven, The Netherlands. She grew up in Westerhoven. In 1994 she completed high school (Athenaeum) at the Hertog Jan College in Valkenswaard. After graduating, she studied Dutch language at the University of Amsterdam.

In 1995 Jessica started Medical School in Maastricht. She was committed to the quality of the Medical School program as chair of the student advisory board and vicechair of the Medical School program committee together with Prof. Ton F. P. M. de Goeij. She also worked as a research assistant with Prof. Herman Kingma at the Department of Ear, Nose and Throat Surgery, Clinical Vestibulology; Maastricht University Medical Center. In addition, she completed internships abroad at the Department of Pediatric Oncology in Debrecen, Hungary and the Department of Gynecology in Bulawayo, Zimbabwe.

In 1999, she was asked by astronaut Prof. Laurence R. Young to participate in a research project at the Man Vehicle Laboratory at the Department of Aeronautics and Astronautics at the Massachusetts Institute of Technology (MIT) in Cambridge, United States. The aim of the research project was to investigate the impact of artificial gravity during short-radius centrifugation on the vestibular organ in astronauts and subjects. She also took courses in Space Medicine and Human Factors at MIT and Neuroscience at Harvard Medical School in Boston, United States. In addition, she was member of the "Go Mars" club, a group of enthusiastic MIT and Harvard students and professors including Prof. Buzz Aldrin, who discussed future flights to and life on Mars.

She transferred to Medical School in Leiden and obtained her medical degree in 2001.

For a year, in 2002, she travelled around the world with her current husband Tjebbe. Together they experienced a fantastic time in Indonesia, Australia, New Zealand, Thailand, Myanmar, Laos, Cambodia, Vietnam and China.

In 2003 she started as a resident (not in training) at the Department of Cardio - Thoracic Surgery at the Amsterdam Medical Center (AMC), now part of Amsterdam University Medical Centers (Amsterdam UMC). She was accepted as a resident Surgery (in training) at the AMC and Sint Lucas Andreas Hospital in 2003 and completed the first two years. In 2006, she transferred to Rehabilitation Medicine at the VU medical center, now part of Amsterdam UMC and Rehabilitation center Heliomare. She followed an in-depth training in Pediatric Rehabilitation Medicine with Prof. Jules Becher and graduated as a medical specialist in Rehabilitation Medicine in 2011. In that same year, Jessica started as a pediatric rehabilitation physician at Rehabilitation center Reade in Amsterdam. Together with Suzanne Willems and Frank Voskuilen, she set up the pediatric rehabilitation team of mytylschool "de Regenboog" (nowadays "de Parel"). She also worked at Reade - Pediatric rehabilitation outpatient clinics Overtoom; Reade - Therapeutic toddler groups 0-4 years; mytylschool Drostenburg and Nifterlake.

In 2015, Jessica started as a pediatric rehabilitation physician at the Department of Rehabilitation Medicine of Amsterdam UMC, now under the leadership of Prof. Vincent de Groot. Jessica is specialized in the treatment of children and adolescents with Heritable Connective Tissue Disorders. She is part of the Amsterdam UMC - expert center Marfan syndrome and related disorders, led by Dr. Maarten Groenink, Dr. Marieke J.H. Baars and Dr. Leonie A. Menke. Jessica is chair of the Dutch Network Marfan and related disorders and member of the European Reference Network Skin. In addition, she is part of the Amsterdam UMC - expert center Cerebral Palsy, led by Prof. Annemieke I. Buizer and member of the expert team for operative indication of children and adolescents with a spastic upper limb. Furthermore, she is member of the expert team for children and adolescents with congenital malformations of the upper limb. She also contributes to the Follow Me – multidisciplinary follow up care program of the Emma's Children's Hospital, Amsterdam UMC, led by Prof. Jaap Oosterlaan.

The Follow You research group started in 2017 under the leadership of Prof. Raoul H. H. Engelbert, as well as this PhD trajectory.

Jessica aims to create a stimulating research, educational and work environment in the field of Pediatric Rehabilitation Medicine together with Prof. Raoul H. H. Engelbert, Prof. Annemieke I. Buizer, the Amsterdam UMC - Pediatric Rehabilitation team, the Follow You research group, researchers, physicians, allied health professionals and patient associations. To this end, new research and educational projects can be developed. She also aims to improve and expand collaboration with other research groups and expert centers in The Netherlands, Europe and worldwide. This contributes to the optimization of medical care, functioning and health of children and adolescents with Heritable Connective Tissue Disorders and other chronic diseases.

Jessica lives in Zandvoort with her husband Tjebbe Warnink, her son Daan (2007), her two daughters Annebel (2009) and Rosa (2014). She loves the sea, the mountains, kitesurfing, snowboarding, travelling, music, theater, dining, and parties at the beach with her family and friends.

Fotograaf: Anita Edridge (2021)

About the author in Dutch - Over de schrijver

Jessica Warnink-Kavelaars is geboren op 26 september 1975 in Eindhoven, Nederland. Zij groeide op in Westerhoven. In 1994 voltooide zij het atheneum aan het Hertog Jan College in Valkenswaard. Daarna studeerde zij Nederlandse Taal en Letterkunde aan de Universiteit van Amsterdam en behaalde haar propedeuse. In 1995 startte zij de opleiding Geneeskunde aan de Universiteit van Maastricht. Zij maakt zich sterk voor de kwaliteit van de opleiding als voorzitter van de studentenadviesraad en als vicevoorzitter van de opleidingscommissie samen met prof. dr. Ton F. P. M. de Goeij. Verder werkte zij als onderzoeksassistent bij prof. dr. Herman Kingma, afdeling Keel-, Neus-, Oorheelkunde, Klinische Vestibulologie, Maastricht Universitair Medisch Centrum. Ook heeft ze buitenlandse stages gedaan bij de afdeling kinderoncologie in Debrecen, Hongarije en bij de afdeling gynaecologie in Bulawayo, Zimbabwe.

In 1999 werd zij gevraagd door astronaut prof. dr. Laurence R. Young om deel te nemen aan een onderzoeksproject van het Man Vehicle Laboratorium, afdeling Lucht- en Ruimtevaarttechniek aan Massachusetts Institute of Technology (MIT) in Cambridge, Verenigde Staten. Het doel van de studie was om het effect van kunstmatige zwaartekracht, door centrifugatie, op het evenwichtsorgaan bij astronauten en proefpersonen te onderzoeken. Ook volgde Jessica de studies Ruimtegeneeskunde en Human Factors aan MIT en Neurowetenschappen aan Harvard Medical School in Boston, Verenigde Staten. Daarnaast was ze lid van de "Go Mars" club, een groep enthousiaste MIT en Harvard studenten en professoren waaronder astronaut prof. dr. Buzz Aldrin. Samen discussieerden zij over toekomstige vluchten en leven op Mars.

In 2000 startte Jessica haar co-schappen aan de Universiteit van Leiden en behaalde in 2001 haar artsendiploma.

Een jaar lang, in 2002, reisde ze met haar huidige echtgenoot Tjebbe de wereld rond. Samen beleefden ze een fantastische tijd in Indonesië, Australië, Nieuw-Zeeland, Thailand, Myanmar, Laos, Cambodja, Vietnam en China.

In 2003 begon Jessica aan haar eerste baan als arts (niet in opleiding tot specialist) op de afdeling Cardio - Thoracale Chirurgie in het Amsterdam Medisch Centrum (AMC), tegenwoordig onderdeel van Amsterdam Universitair Medische Centra (Amsterdam UMC). In 2003 werd zij aangenomen als arts in opleiding tot specialist Chirurgie in het AMC en het Sint Lucas Andreas ziekenhuis. Zij rondde haar eerste twee jaar af. In 2006 startte Jessica de opleiding tot specialist Revalidatiegeneeskunde in het VU Medisch Centrum, tegenwoordig onderdeel van Amsterdam UMC, en revalidatiecentrum Heliomare. Ze volgde een verdieping in de kinderrevalidatie bij prof. dr. Jules Becher en rondde haar opleiding af in 2011. Hetzelfde jaar startte Jessica als kinderrevalidatiearts bij revalidatiecentrum Reade in Amsterdam. Bij mytylschool "de Regenboog" (tegenwoordig "de Parel") heeft zij samen met Suzanne Willems en Frank Voskuilen het kinderrevalidatie-team opgezet. Tevens werkte zij bij Reade - Kinderrevalidatie polikliniek Overtoom, Reade - Therapeutische peutergroepen 0-4 jaar, mytylschool Drostenburg en gespecialiseerd kinderdagverblijf Nifterlake.

In 2015 is Jessica gestart bij de afdeling Revalidatiegeneeskunde in Amsterdam UMC, nu onder leiding van prof. dr. Vincent de Groot. Ze is gespecialiseerd in kinderen en jongeren met erfelijke bindweefsel aandoeningen en maakt deel uit van het Amsterdam UMC - expertisecentrum Marfan en aanverwante aandoeningen, onder leiding van dr. Maarten Groenink, dr. Marieke J.H. Baars en dr. Leonie A. Menke. Daarnaast is Jessica voorzitter van het Nederlandse expertisenetwerk Marfan en aanverwante aandoeningen en lid van het Europese Referentie Netwerk Skin. Ook maakt Jessica deel uit van het Amsterdam UMC - expertisecentrum Cerebrale Parese, onder leiding van prof. dr. Annemieke I. Buizer; expertiseteam - Operatieve indicatiestelling voor kinderen en jongeren met spasticiteit van de bovenste extremiteit en is onderdeel van het expertiseteam - Congenitale arm/hand afwijkingen van de bovenste extremiteit. Tevens draagt ze bij aan het Follow Me -

multidisciplinaire follow up zorgprogramma van het Emma Kinderziekenhuis leiding van prof. dr. Jaap Oosterlaan.

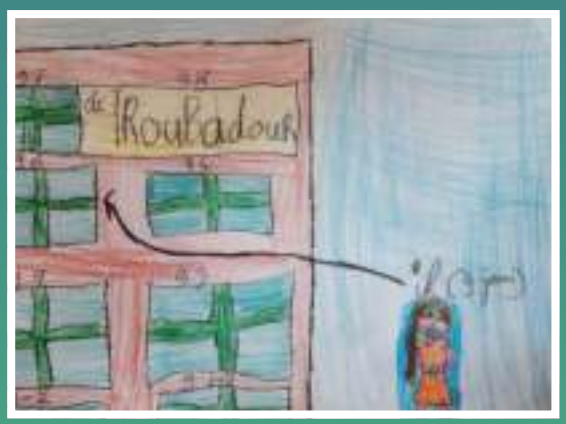
In 2017 is de Follow You onderzoeksgroep gestart onder leiding van prof. dr. Raoul H. H. Engelbert evenals dit promotie traject.

Jessica heeft als doel om samen met prof. dr. Raoul H. H. Engelbert, prof. dr. Annemieke Buizer, het Amsterdam UMC - Kinderrevalidatieteam, de Follow You onderzoeksgroep, onderzoekers, artsen, paramedici en patiëntenorganisaties een stimulerende onderzoeks- onderwijs- en werkomgeving te creëren op het gebied van de kinderrevalidatie. Zo kunnen nieuwe en interessante ideeën, onderzoeks- en onderwijsprojecten ontwikkeld worden. Ook wil zij de samenwerking met andere onderzoeksgroepen en expertisecentra Marfan en aanverwante aandoeningen in Nederland, Europa en wereldwijd versterken en uitbreiden. Dit draagt bij aan het optimaliseren van de medische zorg en het functioneren en de gezondheid van kinderen en adolescenten met erfelijke bindweefsel aandoeningen en andere chronische ziekten.

Jessica Warnink-Kavelaars woont in Zandvoort met haar man Tjebbe Warnink, haar zoon Daan (2007) en haar dochters Annebel (2009) en Rosa (2014). Ze houdt van de zee, de bergen, kitesurfen, snowboarden, reizen, muziek, theater, dineren en feestjes op het strand met haar familie en vrienden.

“ Me and my family” by Rosa Warnink (7 years)


SPORT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