Psychosocial well-being in pediatric heart disease

toward innovative interventions

Malindi van der Mheen

Psychosocial Well-being in Pediatric Heart Disease:

Toward Innovative Interventions

Malindi van der Mheen

COLOFON

Psychosocial Well-being in Pediatric Heart Disease: Toward Innovative Interventions, Malindi van der Mheen

Cover and chapter pages design by Linda Steenwijk, Studio Kuukeluus
Layout and design by Anna Bleeker, persoonlijkproefschrift.nl.
Printed by Ipskamp Printing, proefschriften.net

Psychosocial Well-being in Pediatric Heart Disease:
Toward Innovative Interventions

Psychosociaal welbevinden van kinderen met een hartaandoening:
Naar innovatieve interventies

Proefschrift

Ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof. dr. R.C.M.E. Engels
en volgens het besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
dinsdag 26 mei 2020 om 15:30 uur

door:

Malindi van der Mheen

geboren op woensdag 4 september 1991
te Almelo

Erasmus University Rotterdam

PROMOTIECOMMISSIE

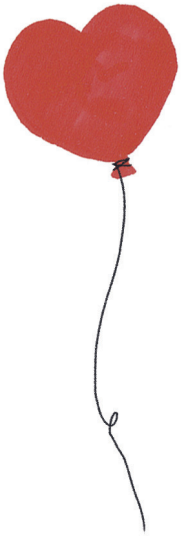
Promotoren:
Prof. dr. E.M.W.J. Utens
Prof. dr. M.H.J. Hillegers

Overige leden:
Prof. dr. K.F.M. Joosten
Prof. dr. M.A. Grootenhuis
Prof. dr. E.M. van de Putte

Copromotor:
Dr. I.M. van Beynum

Paranimfen:
José Hordijk
Robin Eijlers

TABLE OF CONTENTS



1

CHAPTER 1

General introduction

PEDIATRIC HEART DISEASE

The term "pediatric heart disease" covers a range of heart conditions in children. Pediatric heart disease can be congenital (i.e., present from birth) or acquired (i.e., developed after birth).

Congenital heart defects

Congenital heart defects (CHDs) encompass multiple structural abnormalities of the heart and/or intrathoracic great vessels which, by definition, arise before birth [1]. Affecting approximately 8 out of 1,000 live births, congenital heart disease is the most common birth defect [2-6]. CHDs range from simple (e.g., patent ductus arteriosus, atrial and ventricular septal defects) to more complex (e.g., hypoplastic left heart syndrome, transposition of the great arteries). Consequently, CHDs are asymptomatic or cause a variety of clinical symptoms, such as shortness of breath, cyanosis, edema, impaired growth, and decreased exercise capacity. Despite the tremendous improvement in preventive care and diagnostic and therapeutic interventions (e.g., heart surgery, catheter interventions, or drug therapy) and subsequent improvement in survival rates [7], CHDs still are a leading cause of infant mortality in the Western world [8-10]. Estimates now indicate that 95% of children with a simple CHD, 90% of children with a moderately severe CHD, and 80% of children with a complex CHD survive into adulthood [11, 12].

Cardiomyopathy

Cardiomyopathies are acquired myocardial disorders (i.e., affecting the heart muscle) characterized by structural and functional abnormalities of the heart. Cardiomyopathies are approximately 700 times less prevalent than CHDs [13]. Dilated cardiomyopathy (DCM) is the most common subtype, accounting for approximately 60% of cardiomyopathies [13, 14]. The two other main subtypes are restrictive and hypertrophic cardiomyopathy. In DCM, systolic function is impaired and the left ventricle is dilated [15]. Estimates of annual incidence rates of DCM range from 0.57 [16] to 0.73 [14] per 100,000 children. In the majority of children, the cause of DCM is unknown (i.e., "idiopathic"). The cause of DCM can also be genetic or multifactorial [17, 18]. There is a wide spectrum of symptoms, ranging from asymptomatic to arrhythmias and/or depressed exercise capacity, progressing to heart failure or sudden death [19]. The prognosis of DCM is poor: the two-year transplant-free survival rate equals approximately 60% [16]. DCM is the leading indication for cardiac transplantation worldwide [20-22].

PSYCHOSOCIAL PROBLEMS IN PEDIATRIC HEART DISEASE

Considering the somatic symptoms, the single or multiple invasive interventions, and medical treatment of CHDs and DCM, a substantial impact on psychosocial well-being of affected children and their parents and siblings can be expected. Psychosocial well-being is a broad concept which encompasses aspects of health on the following domains:

- emotions;
- behavior;
- social functioning;
- cognitive functioning;
- and family functioning.

Psychosocial problems in children with CHDs

Due to tremendous medical advances, as previously mentioned, survival rates of children with CHDs have greatly increased over the past decades [7]. Even in complex CHDs, adults nowadays outnumber children [6]. CHDs have become a chronic condition affecting individuals of all ages rather than a predominantly pediatric disease, which has caused a shift from acute treatment to long-term care, including the assessment of psychosocial well-being. Therefore, numerous studies have examined the psychosocial well-being of children with CHDs. Accumulating evidence has shown that children with CHDs are at increased risk of a range of psychosocial problems, encompassing multiple domains of their lives [23, 24].

Posttraumatic stress. Children with CHDs undergo medical procedures such as cardiac catheterization, heart surgery, thoracic drains, other invasive procedures, and magnetic resonance imaging scans. Understandably, this causes significant acute stress in most children [25]. In the majority of children, stress decreases spontaneously after a medical procedure or hospitalization [26, 27]. Still, approximately 12% of children with CHDs show elevated posttraumatic stress symptoms 4 to 8 weeks after cardiac surgery [28, 29], such as flashbacks, avoidance of reminders of the traumatic event, sleeping problems, and hypervigilance [30, 31]. If such symptoms are persistent and result in significant distress, a child can eventually be diagnosed with a posttraumatic stress disorder (PTSD) [30]. Approximately 12% [29] to 29% [32] of children and adolescents with CHDs develop a PTSD after cardiac surgery [28]. PTSD is associated with emotional and behavioral problems [28], decreased therapy compliance [31, 33], impaired quality of life [34, 35], and increased use of health care services [36].

Emotional and behavioral functioning. Emotional and behavioral problems have already been reported in infants with CHDs, who more often show symptoms of irritability and lethargy and are more often difficult to soothe [37, 38]. As reported by parents and teachers, preschool and school-age children with CHDs are at risk of internalizing (i.e., anxiety, depression) and externalizing (i.e., aggression, hyperactivity) problems [39-41]. If left untreated, these problems may persist into adolescence and adulthood and may convert to psychiatric disorders. As to adolescents with CHDs, parents [23, 24, 42] and adolescents themselves [43] mainly report internalizing problems such as depression, loneliness, and anxiety [44-46].

Social functioning. Though contradictory results have been found [47], in general, physical activity levels of children with CHDs seem to be reduced compared to their healthy peers [48-50]. This may have a negative impact, as reduced levels of physical activity and exercise capacity have been found to be associated with a lower quality of life in children with CHDs [48]. Moreover, reduced exercise capacity decreases children's capacity to play and engage in social physical activities, which limits their opportunities to develop their social skills [51]. Indeed, in general, children and adolescents with CHDs participate less in social activities [52, 53]. Children and adolescents [53] with CHD tend to be perceived as more withdrawn, less accepted by peers, and too dependent on others [54]. Also, multiple studies have reported impaired social functioning and deficits in social cognition [54-60].

Cognitive functioning. Several systematic reviews [24, 55, 56, 61-63] and meta-analyses [23, 64] have shown that children with CHDs, particularly children with hypoplastic left heart syndrome [55, 65, 66], are at increased risk of a range of neuropsychological deficits. These deficits may be attributed to pre-operative and perioperative factors, such as reduced blood flow and oxygenation of the brain in utero and after birth [24, 56, 67] and vital organ support during surgery [24]. More extensive reviews of possible causes of neuropsychological deficits in CHD are provided by Marino et al. [24], Cassidy et al. [56], and Nattel et al. [67]. Though the level of neuropsychological deficits may vary by disease complexity, children with CHDs show problems on various domains of executive functioning (i.e., higher-order thinking skills) [55, 59, 68-72], attention [73-76], memory [70, 77-80], visuospatial skills [70, 79-81], and language [76, 82]. These neuropsychological deficits can lead to school problems and have a negative impact on academic achievement [83, 84]. Indeed, reduced levels of school performance and academic outcomes have been reported for all types of CHD [42, 54, 55, 85-87]. Moreover, rates of

grade repetition [41, 68, 73, 75, 88, 89], use of remedial teaching and academic tutoring [70, 73, 75, 90], and attendance of special education [52, 70, 75, 90] are higher in children with CHDs than in their healthy peers. Neuropsychological and psychosocial difficulties associated with childhood CHD often persist into adolescence and adulthood [53, 57, 61, 91-93], and negatively affect educational and occupational status, employability, lifelong earnings, insurability, and quality of life [94-100].

Family functioning. CHD not only affects the psychosocial well-being of the child itself, but also impacts other family members. Parents, mothers in particular, are at risk of several psychosocial problems [101, 102]. Increased levels of mental health problems have been found, such as depression and anxiety symptoms [102]. Parents also experience elevated levels of parenting stress [39] and adjustment problems and have a lower quality of life than parents of healthy children [103, 104]. Such difficulties are more profound shortly after diagnosis [102, 103, 105] and in the months following cardiac surgery [102, 106], but remain present on the long-term [103, 107-109]. Moreover, approximately 30% of parents experience symptoms of posttraumatic stress or even meet the diagnostic criteria of a posttraumatic stress disorder [106, 110]. Families are also confronted with practical problems such as financial burdens [102, 111] and CHD negatively impacts parents' employment due to caregiving and hospital appointments [111].

Siblings of chronically ill children are often overlooked [112, 113]. Little research has been done specifically into the psychosocial well-being of siblings of children with CHDs. However, the available studies have demonstrated that siblings may be negatively affected as well [39, 114, 115]. Moreover, according to meta-analyses [116, 117], the psychosocial well-being of siblings of chronically ill children is negatively affected, although to a lesser extent than the psychosocial well-being of the chronically ill child itself. Siblings are especially at risk of internalizing problems [117].

Psychosocial problems in children with DCM

It is well-established that adults with heart failure show increased levels of anxiety and depression [118, 119]. Moreover, in these adults, anxiety and depression predict adverse clinical outcomes such as hospitalization and mortality [118, 120-125]. Regarding psychosocial well-being in children with DCM, however, very little research has been done. The available pediatric studies have mainly focused on health-related quality of life, which has been reported to be lower for children

with DCM than for their healthy peers [126-129]. Furthermore, two studies have shown that physical health-related quality of life predicts mortality and cardiac transplantation in children with DCM [127, 129]. Regarding other aspects of psychosocial well-being, two studies with limited sample sizes (n ≤ 19) have reported conflicting results as to emotional and behavioral problems in children with DCM [130, 131]. Considering the scarcity of research in this domain, in the current thesis we aimed to examine the level of emotional and behavioral problems in children with DCM compared to the general population.

PSYCHOSOCIAL INTERVENTIONS IN PEDIATRIC HEART DISEASE

Considering the psychosocial problems that children with CHDs and their families experience, evidence-based psychosocial interventions are needed. It is widely acknowledged that a psychosocial intervention for children with CHDs should be provided by a multidisciplinary team on a family-centered level [106, 132-137]. Parental psychosocial functioning is known to be an important mediator in children's well-being [102, 134, 135]. Maternal mental health and worry have even appeared to be more important predictors of children's psychosocial well-being than illness severity [134, 138, 139]. Unfortunately, as discussed previously, parents of children with CHDs are at risk of psychosocial problems themselves [39, 101-110]. Therefore, parents should be actively involved in psychosocial interventions.

Furthermore, developmental milestones present more difficulties for children with CHDs and their families than for their healthy peers [56, 140]. An important milestone is the developmental transition of starting school, considering the emotional and cognitive vulnerability and the difficulties concerning exercise capacity and social development. Providing intervention to young children has several benefits [51]. Difficulties may be easier to solve, because they are likely less ingrained and neuroplasticity in young children is high [141]. Also, by intervening early, the negative impact on further development can be minimized [141-143]. Therefore, the psychosocial intervention should be attuned to young children who are in the developmental transition of starting school.

CHIP-interventions to improve psychosocial well-being of young children with CHDs and their families

At the start of our project, worldwide, the only scientifically examined psychosocial intervention for young children with CHDs who are starting school was the Congenital Heart Disease Intervention Program – School (CHIP-School) [134].

CHIP-School targeted parents of young children with CHDs who were entering school. The intervention consisted of a one-day multidisciplinary group workshop and a follow-up appointment with a clinical psychologist. The theoretical rationale of CHIP-School was based on Thompson's transactional stress and coping model [144] which states that the effect of illness factors on a child's psychosocial well-being is mediated by familial, especially maternal, coping and appraisal. By strengthening parental mental health and parenting skills through CHIP-School, it was aimed to indirectly increase the emotional resilience of children with CHDs. CHIP-School significantly improved maternal mental health, perceived strain on the family, and school absence of the child. However, no significant improvements were found as to child psychosocial well-being.

In this thesis, we aimed to improve the effectiveness of CHIP-School by extending and innovating the program. As CHIP-School only consisted of a parent module, we expected that the obtained results could be improved by including a child module, thereby also aiming to directly improve children's resilience and psychosocial well-being. For this reason, we extended the CHIP-School program by adding a specific child module for children with CHDs and their siblings, thereby creating "CHIP-Family".

We integrated elements of the cognitive behavioral Fun FRIENDS protocol [145] into the child module. Fun FRIENDS was originally developed for 4-year-old to 7-year-old children with anxiety disorders. The Fun FRIENDS program aims to increase emotional resilience, social-emotional skills, and coping skills, and to decrease emotional and behavioral problems; especially anxiety and depressive symptoms. The effectiveness of Fun FRIENDS has been shown in two large preventive, classroom-based studies [146, 147]. In clinical samples, the program has been insufficiently examined, although three small studies show promising results [148-150]. In this thesis, we also conducted a clinical open trial to examine whether anxiety problems in young children with anxiety disorders improved after completing the Fun FRIENDS program.

EMDR treatment for medically-related posttraumatic stress symptoms

Apart from a psychosocial intervention to improve the overall psychosocial well-being of children with CHDs, an effective intervention specifically targeting posttraumatic stress symptoms and PTSD in children with pediatric heart disease is needed. Eye movement desensitization and reprocessing (EMDR) offers promising results [151]. The EMDR treatment method is based on bilateral stimulation whilst

processing memories of traumatic experiences [151]. Advantages of EMDR are that it does not require detailed descriptions of the traumatic event, extended exposure, or homework [152]. Moreover, it appears to be an efficient treatment method requiring relatively little time and costs [153, 154]. In adults, EMDR is well-established as an effective treatment for posttraumatic stress symptoms and PTSD [155-157]. In child populations with trauma's caused by abuse, violence, or natural disasters, EMDR has shown promising results [158, 159]. In children with CHDs, however, EMDR has not been examined yet [28], which is alarming considering the high previously reported prevalence rates of posttraumatic stress symptoms and PTSD [28, 29, 32]. For this reason, in this thesis, we aimed to examine the effectiveness of EMDR in treating medically-related posttraumatic stress symptoms.

AIMS AND OUTLINE OF THIS THESIS

In Chapter 2, we describe the results of a small open trial in which we provided the cognitive behavioral Fun FRIENDS program to a clinical sample of young children with anxiety disorders. Our aim was to examine whether these children showed less anxiety after participating in Fun FRIENDS. As stated, we integrated components of the Fun FRIENDS protocol into the child module of the psychosocial CHIP-Family program for young children with CHDs and their families. In Chapter 3, we elaborate on the content of CHIP-Family and describe the rationale and design of our randomized controlled trial into the effectiveness of the CHIP-Family program. Subsequently, in Chapter 4, we present the results regarding the effectiveness of CHIP-Family. We aimed to investigate the effect of CHIP-Family on the psychosocial well-being of young children with CHDs and their families.

In Chapter 5, we study emotional and behavioral problems in children with DCM. More specifically, we studied the frequency of emotional and behavioral problems in children with DCM compared to normative data. Furthermore, we investigated whether anxiety and depressive problems in children with DCM predicted cardiac transplantation or mortality.

In Chapter 6, we describe the results of a randomized controlled trial into the effectiveness of EMDR in children with medically-related subthreshold (i.e. subclinical) PTSD. We examined whether EMDR was effective in treating posttraumatic stress symptoms, depression, anxiety, and sleep problems in children

who had been hospitalized because of a CHD and in children had been admitted to an emergency department because of acute illness or injury.

Finally, in Chapter 7, we discuss our findings, clinical implications, remaining questions, and propose directions for future research.

REFERENCES

1. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002; 39(12): 1890-900.
2. Reller MD, Strickland MJ, Riehle-Colarusso T, Mahle WT, Correa A. Prevalence of congenital heart defects in metropolitan Atlanta, 1998-2005. J Pediatr. 2008; 153(6): 807-13.
3. Bernier PL, Stefanescu A, Samoukovic G, Tchervenkov CI. The challenge of congenital heart disease worldwide: epidemiologic and demographic facts. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2010; 13(1): 26-34.
4. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol. 2011; 58(21): 2241-7.
5. Dolk H, Loane M, Garne E, European Surveillance of Congenital Anomalies Working G. Congenital heart defects in Europe: prevalence and perinatal mortality, 2000 to 2005. Circulation. 2011; 123(8): 841-9.
6. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. Circulation. 2014; 130(9): 749-56.
7. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. J Am Coll Cardiol. 2010; 56(14): 1149-57.
8. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. 2013; 127(1): e6-e245.
9. Moller JH. Prevalence and incidence of cardiac malformation. In: Moller JH, W.A. N, editors. Perspectives in Pediatric Cardiology: Surgery of Congenital Heart Disease: Pediatric Cardiac Care Consortium, 1984-1995. Armonk, NY: Futura Publishing; 1998. p. 19-26.
10. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation. 2012; 125(1): e2-e220.
11. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JI, et al. Task force 1: the changing profile of congenital heart disease in adult life. J Am Coll Cardiol. 2001; 37(5): 1170-5.
12. Best KE, Rankin J. Long-Term Survival of Individuals Born With Congenital Heart Disease: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2016; 5(6).
13. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med. 2003; 348(17): 1647-55.

14. Nugent AW, Daubeney PE, Chondros P, Carlin JB, Cheung M, Wilkinson LC, et al. The epidemiology of childhood cardiomyopathy in Australia. N Engl J Med. 2003; 348(17): 1639-46.

15. Jefferies JL, Towbin JA. Dilated cardiomyopathy. Lancet. 2010; 375(9716): 752-62.

16. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA. 2006; 296(15): 1867-76.

17. Kimura A. Contribution of genetic factors to the pathogenesis of dilated cardiomyopathy: the cause of dilated cardiomyopathy: genetic or acquired? (genetic-side). Circ J. 2011; 75(7): 1756-65; discussion 65.

18. Yoshikawa T. Contribution of acquired factors to the pathogenesis of dilated cardiomyopathy. -The cause of dilated cardiomyopathy: genetic or acquired? (Acquired-Side). Circ J. 2011; 75(7): 1766-73; discussion 73.

19. Weintraub RG, Semsarian C, Macdonald P. Dilated cardiomyopathy. Lancet. 2017; 390(10092): 400-14.

20. Boucek MM, Waltz DA, Edwards LB, Taylor DO, Keck BM, Trulock EP, et al. Registry of the International Society for Heart and Lung Transplantation: ninth official pediatric heart transplantation report--2006. J Heart Lung Transplant. 2006; 25(8): 893-903.

21. Kirk R, Dipchand AI, Rosenthal DN, Addonizio L, Burch M, Chrisant M, et al. The International Society for Heart and Lung Transplantation Guidelines for the management of pediatric heart failure: Executive summary. [Corrected]. J Heart Lung Transplant. 2014; 33(9): 888-909.

22. Rossano JW, Cherikh WS, Chambers DC, Goldfarb S, Khush K, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Twentieth Pediatric Heart Transplantation Report-2017; Focus Theme: Allograft ischemic time. J Heart Lung Transplant. 2017; 36(10): 1060-9.

23. Karsdorp PA, Everaerd W, Kindt M, Mulder BJ. Psychological and cognitive functioning in children and adolescents with congenital heart disease: a meta-analysis. J Pediatr Psychol. 2007; 32(5): 527-41.

24. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012; 126(9): 1143-72.

25. Ari AB, Peri T, Margalit D, Galili-Weisstub E, Udassin R, Benarroch F. Surgical procedures and pediatric medical traumatic stress (PMTS) syndrome: Assessment and future directions. J Pediatr Surg. 2018; 53(8): 1526-31.

26. Kahana SY, Feeny NC, Youngstrom EA, Drotar D. Posttraumatic stress in youth experiencing illnesses and injuries: an exploratory meta-analysis. Traumatology. 2006; 12(2): 148-61.

27. Kassam-Adams N, Marsac ML, Hildenbrand A, Winston F. Posttraumatic stress following pediatric injury: update on diagnosis, risk factors, and intervention. JAMA Pediatr. 2013; 167(12): 1158-65.

28. Meentken MG, van Beynum IM, Legerstee JS, Helbing WA, Utens EM. Medically Related Post-traumatic Stress in Children and Adolescents with Congenital Heart Defects. Front Pediatr. 2017; 5: 20.

29. Connolly D, McClowry S, Hayman L, Mahony L, Artman M. Posttraumatic stress disorder in children after cardiac surgery. J Pediatr. 2004; 144(4): 480-4.

30. Association AP. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). Washington, DC: American Psychiatric Publishing; 2013.

31. Kazak AE, Kassam-Adams N, Schneider S, Zelikovsky N, Alderfer MA, Rourke M. An integrative model of pediatric medical traumatic stress. J Pediatr Psychol. 2006; 31(4): 343-55.

32. Toren P, Horesh N. Psychiatric morbidity in adolescents operated in childhood for congenital cyanotic heart disease. J Paediatr Child Health. 2007; 43(10): 662-6.

33. Shemesh E, Lurie S, Stuber ML, Emre S, Patel Y, Vohra P, et al. A pilot study of posttraumatic stress and nonadherence in pediatric liver transplant recipients. Pediatrics. 2000; 105(2): E29.

34. Landolt MA, Vollrath ME, Gnehm HE, Sennhauser FH. Post-traumatic stress impacts on quality of life in children after road traffic accidents: prospective study. Aust N Z J Psychiatry. 2009; 43(8): 746-53.

35. Zatzick DF, Jurkovich GJ, Fan MY, Grossman D, Russo J, Katon W, et al. Association between posttraumatic stress and depressive symptoms and functional outcomes in adolescents followed up longitudinally after injury hospitalization. Arch Pediatr Adolesc Med. 2008; 162(7): 642-8.

36. Marsac ML, Cirilli C, Kassam-Adams N, Winston FK. Post-injury medical and psychosocial care in children: Impact of traumatic stress symptoms. Children's Health Care. 2011; 40(2): 116-29.

37. Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B, Rohlicek C, Tchervenkov C, et al. Functional limitations in young children with congenital heart defects after cardiac surgery. Pediatrics. 2001; 108(6): 1325-31.

38. Torowicz D, Irving SY, Hanlon AL, Sumpter DF, Medoff-Cooper B. Infant temperament and parental stress in 3-month-old infants after surgery for complex congenital heart disease. J Dev Behav Pediatr. 2010; 31(3): 202-8.

39. Brosig CL, Mussatto KA, Kuhn EM, Tweddell JS. Psychosocial outcomes for preschool children and families after surgery for complex congenital heart disease. Pediatr Cardiol. 2007; 28(4): 255-62.

40. Glanzman MM, Licht D, Wernovsky G. Neurodevelopment in children with complex congenital heart disease. In: Gleason MM, Rychick J, Shaddy RE, editors. Pediatric practice: Cardiology. New York, NY: McGraw-Hill; 2011.

41. Bellinger DC, Newburger JW, Wypij D, Kuban KC, duPlesssis AJ, Rappaport LA. Behaviour at eight years in children with surgically corrected transposition: The Boston Circulatory Arrest Trial. Cardiol Young. 2009; 19(1): 86-97.

42. Hovels-Gurich HH, Konrad K, Skorzenski D, Minkenberg R, Herpertz-Dahlmann B, Messmer BJ, et al. Long-term behavior and quality of life after corrective cardiac surgery in infancy for tetralogy of Fallot or ventricular septal defect. Pediatr Cardiol. 2007; 28(5): 346-54.

43. Uzark K, Jones K, Slusher J, Limbers CA, Burwinkle TM, Varni JW. Quality of life in children with heart disease as perceived by children and parents. Pediatrics. 2008; 121(5): e1060-7.

44. DeMaso DR, Labella M, Taylor GA, Forbes PW, Stopp C, Bellinger DC, et al. Psychiatric disorders and function in adolescents with d-transposition of the great arteries. J Pediatr. 2014; 165(4): 760-6.

45. Freitas IR, Castro M, Sarmento SL, Moura C, Viana V, Areias JC, et al. A cohort study on psychosocial adjustment and psychopathology in adolescents and young adults with congenital heart disease. BMJ Open. 2013; 3(1).

46. Holland JE, Cassidy AR, Stopp C, White MT, Bellinger DC, Rivkin MJ, et al. Psychiatric Disorders and Function in Adolescents with Tetralogy of Fallot. J Pediatr. 2017; 187: 165-73.

47. Voss C, Duncombe SL, Dean PH, de Souza AM, Harris KC. Physical Activity and Sedentary Behavior in Children With Congenital Heart Disease. J Am Heart Assoc. 2017; 6(3).

48. Dulfer K, Helbing WA, Duppen N, Utens EM. Associations between exercise capacity, physical activity, and psychosocial functioning in children with congenital heart disease: a systematic review. Eur J Prev Cardiol. 2014; 21(10): 1200-15.

49. Massin MM, Hovels-Gurich HH, Gerard P, Seghaye MC. Physical activity patterns of children after neonatal arterial switch operation. Ann Thorac Surg. 2006; 81(2): 665-70.

50. McCrindle BW, Williams RV, Mital S, Clark BJ, Russell JL, Klein G, et al. Physical activity levels in children and adolescents are reduced after the Fontan procedure, independent of exercise capacity, and are associated with lower perceived general health. Arch Dis Child. 2007; 92(6): 509-14.

51. McCusker CG, Casey F. Congenital Heart Disease and Neurodevelopment: Understanding and Improving Outcomes. Cambridge: Academic Press; 2016.

52. Farr SL, Downing KF, Riehle-Colarusso T, Abarbanell G. Functional limitations and educational needs among children and adolescents with heart disease. Congenit Heart Dis. 2018; 13(4): 633-9.

53. Schaefer C, von Rhein M, Knirsch W, Huber R, Natalucci G, Caflisch J, et al. Neurodevelopmental outcome, psychological adjustment, and quality of life in adolescents with congenital heart disease. Dev Med Child Neurol. 2013; 55(12): 1143-9.

54. McCusker CG, Armstrong MP, Mullen M, Doherty NN, Casey FA. A sibling-controlled, prospective study of outcomes at home and school in children with severe congenital heart disease. Cardiol Young. 2013; 23(4): 507-16.

55. Martinez-Biarge M, Jowett VC, Cowan FM, Wusthoff CJ. Neurodevelopmental outcome in children with congenital heart disease. Semin Fetal Neonatal Med. 2013; 18(5): 279-85.

56. Cassidy AR, Ilardi D, Bowen SR, Hampton LE, Heinrich KP, Loman MM, et al. Congenital heart disease: A primer for the pediatric neuropsychologist. Child Neuropsychol. 2017: 1-44.

57. Spijkerboer AW, Utens EM, Bogers AJ, Helbing WA, Verhulst FC. A historical comparison of long-term behavioral and emotional outcomes in children and adolescents after invasive treatment for congenital heart disease. J Pediatr Surg. 2008; 43(3): 534-9.

58. Calderon J, Angeard N, Pinabiaux C, Bonnet D, Jambaque I. Facial expression recognition and emotion understanding in children after neonatal open-heart surgery for transposition of the great arteries. Dev Med Child Neurol. 2014; 56(6): 564-71.

59. Calderon J, Bonnet D, Courtin C, Concordet S, Plumet MH, Angeard N. Executive function and theory of mind in school-aged children after neonatal corrective cardiac surgery for transposition of the great arteries. Dev Med Child Neurol. 2010; 52(12): 1139-44.

60. Bellinger DC. Are children with congenital cardiac malformations at increased risk of deficits in social cognition? Cardiol Young. 2008; 18(1): 3-9.

61. Bellinger DC, Newburger JW. Neuropsychological, psychosocial, and quality-of-life outcomes in children and adolescents with congenital heart disease. Prog Pediatr Cardiol. 2010; 29: 87-92.

62. Snookes SH, Gunn JK, Eldridge BJ, Donath SM, Hunt RW, Galea MP, et al. A systematic review of motor and cognitive outcomes after early surgery for congenital heart disease. Pediatrics. 2010; 125(4): e818-27.

63. Mebius MJ, Kooi EMW, Bilardo CM, Bos AF. Brain Injury and Neurodevelopmental Outcome in Congenital Heart Disease: A Systematic Review. Pediatrics. 2017; 140(1).

64. Khalil A, Suff N, Thilaganathan B, Hurrell A, Cooper D, Carvalho JS. Brain abnormalities and neurodevelopmental delay in congenital heart disease: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2014; 43(1): 14-24.

65. Puosi R, Korkman M, Sarajuuri A, Jokinen E, Mildh L, Mattila I, et al. Neurocognitive development and behavioral outcome of 2-year-old children with univentricular heart. J Int Neuropsychol Soc. 2011; 17(6): 1094-103.

66. Brosig C, Mussatto K, Hoffman G, Hoffmann RG, Dasgupta M, Tweddell J, et al. Neurodevelopmental outcomes for children with hypoplastic left heart syndrome at the age of 5 years. Pediatr Cardiol. 2013; 34(7): 1597-604.

67. Nattel SN, Adrianzen L, Kessler EC, Andelfinger G, Dehaes M, Cote-Corriveau G, et al. Congenital Heart Disease and Neurodevelopment: Clinical Manifestations, Genetics, Mechanisms, and Implications. Can J Cardiol. 2017; 33(12): 1543-55.

68. Gerstle M, Beebe DW, Drotar D, Cassedy A, Marino BS. Executive functioning and school performance among pediatric survivors of complex congenital heart disease. 2016; 173: 154-9.

69. Sanz JH, Berl MM, Armour AC, Wang J, Cheng YI, Donofrio MT. Prevalence and pattern of executive dysfunction in school age children with congenital heart disease. Congenit Heart Dis. 2017; 12(2): 202-9.

70. Bellinger DC, Wypij D, Rivkin MJ, DeMaso DR, Robertson RL, Jr., Dunbar-Masterson C, et al. Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure: neuropsychological assessment and structural brain imaging. Circulation. 2011; 124(12): 1361-9.

71. Calderon J, Jambaque I, Bonnet D, Angeard N. Executive functions development in 5- to 7-year-old children with transposition of the great arteries: a longitudinal study. Dev Neuropsychol. 2014; 39(5): 365-84.

72. Cassidy AR, White MT, DeMaso DR, Newburger JW, Bellinger DC. Executive Function in Children and Adolescents with Critical Cyanotic Congenital Heart Disease. J Int Neuropsychol Soc. 2015; 21(1): 34-49.

73. Bellinger DC, Wypij D, duPlessis AJ, Rappaport LA, Jonas RA, Wernovsky G, et al. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: the Boston Circulatory Arrest Trial. J Thorac Cardiovasc Surg. 2003; 126(5): 1385-96.

74. Hovels-Gurich HH, Konrad K, Skorzenski D, Herpertz-Dahlmann B, Messmer BJ, Seghaye MC. Attentional dysfunction in children after corrective cardiac surgery in infancy. Ann Thorac Surg. 2007; 83(4): 1425-30.

75. Shillingford AJ, Glanzman MM, Ittenbach RF, Clancy RR, Gaynor JW, Wernovsky G. Inattention, hyperactivity, and school performance in a population of school-age children with complex congenital heart disease. Pediatrics. 2008; 121(4): e759-67.

76. Miatton M, De Wolf D, Francois K, Thiery E, Vingerhoets G. Neuropsychological performance in school-aged children with surgically corrected congenital heart disease. J Pediatr. 2007; 151(1): 73-8.

77. Cassidy AR, Newburger JW, Bellinger DC. Learning and Memory in Adolescents With Critical Biventricular Congenital Heart Disease. J Int Neuropsychol Soc. 2017; 23(8): 627-39.

78. van der Rijken R, Hulstijn-Dirkmaat G, Kraaimaat F, Nabuurs-Kohrman L, Daniels O, Maassen B. Evidence of impaired neurocognitive functioning in school-age children awaiting cardiac surgery. Dev Med Child Neurol. 2010; 52(6): 552-8.

79. Bellinger DC, Rivkin MJ, DeMaso D, Robertson RL, Stopp C, Dunbar-Masterson C, et al. Adolescents with tetralogy of Fallot: neuropsychological assessment and structural brain imaging. Cardiol Young. 2015; 25(2): 338-47.

80. Bellinger DC, Watson CG, Rivkin MJ, Robertson RL, Roberts AE, Stopp C, et al. Neuropsychological Status and Structural Brain Imaging in Adolescents With Single Ventricle Who Underwent the Fontan Procedure. J Am Heart Assoc. 2015; 4(12).

81. Bellinger DC, Bernstein JH, Kirkwood MW, Rappaport LA, Newburger J. Visual-spatial skills in children after open-heart surgery. J Dev Behav Pediatr. 2003; 24(3): 169-79.

82. Andropoulos DB, Ahmad HB, Haq T, Brady K, Stayer SA, Meador MR, et al. The association between brain injury, perioperative anesthetic exposure, and 12-month neurodevelopmental outcomes after neonatal cardiac surgery: a retrospective cohort study. Paediatr Anaesth. 2014; 24(3): 266-74.

83. Diamond A. Executive functions. Annu Rev Psychol. 2013; 64: 135-68.

84. Calderon J, Bellinger DC. Executive function deficits in congenital heart disease: why is intervention important? Cardiol Young. 2015; 25(7): 1238-46.

85. Oster ME, Watkins S, Hill KD, Knight JH, Meyer RE. Academic Outcomes in Children With Congenital Heart Defects: A Population-Based Cohort Study. Circ Cardiovasc Qual Outcomes. 2017; 10(2).

86. Sarrechia I, Miatton M, De Wolf D, Francois K, Gewillig M, Meyns B, et al. Neurocognitive development and behaviour in school-aged children after surgery for univentricular or biventricular congenital heart disease. Eur J Cardiothorac Surg. 2016; 49(1): 167-74.

87. Cassidy AR, White MT, DeMaso DR, Newburger JW, Bellinger DC. Processing speed, executive function, and academic achievement in children with dextro-transposition of the great arteries: Testing a longitudinal developmental cascade model. Neuropsychology. 2016; 30(7): 874-85.

88. Miatton M, De Wolf D, Francois K, Thiery E, Vingerhoets G. Behavior and self-perception in children with a surgically corrected congenital heart disease. J Dev Behav Pediatr. 2007; 28(4): 294-301.

89. Mahle WT, Clancy RR, Moss EM, Gerdes M, Jobes DR, Wernovsky G. Neurodevelopmental outcome and lifestyle assessment in school-aged and adolescent children with hypoplastic left heart syndrome. Pediatrics. 2000; 105(5): 1082-9.

90. Riehle-Colarusso T, Autry A, Razzaghi H, Boyle CA, Mahle WT, Van Naarden Braun K, et al. Congenital Heart Defects and Receipt of Special Education Services. Pediatrics. 2015; 136(3): 496-504.

91. Holbein CE, Fogleman ND, Hommel K, Apers S, Rassart J, Moons P, et al. A multinational observational investigation of illness perceptions and quality of life among patients with a Fontan circulation. Congenit Heart Dis. 2018; 13(3): 392-400.

92. Kovacs AH, Moons P. Psychosocial functioning and quality of life in adults with congenital heart disease and heart failure. Heart Fail Clin. 2014; 10(1): 35-42.

93. Ringle ML, Wernovsky G. Functional, quality of life, and neurodevelopmental outcomes after congenital cardiac surgery. Semin Perinatol. 2016; 40(8): 556-70.

94. Kovacs AH, Saidi AS, Kuhl EA, Sears SF, Silversides C, Harrison JL, et al. Depression and anxiety in adult congenital heart disease: predictors and prevalence. Int J Cardiol. 2009; 137(2): 158-64.

95. Kovacs AH, Sears SF, Saidi AS. Biopsychosocial experiences of adults with congenital heart disease: review of the literature. Am Heart J. 2005; 150(2): 193-201.

96. Lane DA, Lip GY, Millane TA. Quality of life in adults with congenital heart disease. Heart. 2002; 88(1): 71-5.

97. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, et al. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. Eur Heart J. 2003; 24(7): 673-83.

98. Daliento L, Mapelli D, Russo G, Scarso P, Limongi F, Iannizzi P, et al. Health related quality of life in adults with repaired tetralogy of Fallot: psychosocial and cognitive outcomes. Heart. 2005; 91(2): 213-8.

99. Kamphuis M, Vogels T, Ottenkamp J, Van Der Wall EE, Verloove-Vanhorick SP, Vliegen HW. Employment in adults with congenital heart disease. Arch Pediatr Adolesc Med. 2002; 156(11): 1143-8.

100. Gatzoulis MA. Adult congenital heart disease: education, education, education. Nat Clin Pract Cardiovasc Med. 2006; 3(1): 2-3.

101. Kolaitis GA, Meentken MG, Utens E. Mental Health Problems in Parents of Children with Congenital Heart Disease. Front Pediatr. 2017; 5: 102.

102. Wei H, Roscigno CI, Hanson CC, Swanson KM. Families of children with congenital heart disease: A literature review. Heart Lung. 2015; 44(6): 494-511.

103. Lawoko S, Soares JJ. Psychosocial morbidity among parents of children with congenital heart disease: a prospective longitudinal study. Heart Lung. 2006; 35(5): 301-14.

104. Fonseca A, Nazare B, Canavarro MC. Parental psychological distress and quality of life after a prenatal or postnatal diagnosis of congenital anomaly: a controlled comparison study with parents of healthy infants. Disabil Health J. 2012; 5(2): 67-74.

105. Jackson AC, Frydenberg E, Liang RP, Higgins RO, Murphy BM. Familial impact and coping with child heart disease: a systematic review. Pediatr Cardiol. 2015; 36(4): 695-712.

106. Woolf-King SE, Anger A, Arnold EA, Weiss SJ, Teitel D. Mental Health Among Parents of Children With Critical Congenital Heart Defects: A Systematic Review. J Am Heart Assoc. 2017; 6(2).

107. Solberg O, Dale MT, Holmstrom H, Eskedal LT, Landolt MA, Vollrath ME. Long-term symptoms of depression and anxiety in mothers of infants with congenital heart defects. J Pediatr Psychol. 2011; 36(2): 179-87.

108. Majnemer A, Limperopoulos C, Shevell M, Rohlicek C, Rosenblatt B, Tchervenkov C. Health and well-being of children with congenital cardiac malformations, and their families, following open-heart surgery. Cardiol Young. 2006; 16(2): 157-64.

109. Franck LS, McQuillan A, Wray J, Grocott MP, Goldman A. Parent stress levels during children's hospital recovery after congenital heart surgery. Pediatr Cardiol. 2010; 31(7): 961-8.

110. Helfricht S, Latal B, Fischer JE, Tomaske M, Landolt MA. Surgery-related posttraumatic stress disorder in parents of children undergoing cardiopulmonary bypass surgery: a prospective cohort study. Pediatr Crit Care Med. 2008; 9(2): 217-23.

111. McClung N, Glidewell J, Farr SL. Financial burdens and mental health needs in families of children with congenital heart disease. Congenit Heart Dis. 2018; 13(4): 554-62.

112. Gan LL, Lum A, Wakefield CE, Nandakumar B, Fardell JE. School Experiences of Siblings of Children with Chronic Illness: A Systematic Literature Review. J Pediatr Nurs. 2017; 33: 23-32.

113. Ray LD. Parenting and Childhood Chronicity: making visible the invisible work. J Pediatr Nurs. 2002; 17(6): 424-38.

114. Caris EC, Dempster N, Wernovsky G, Miao Y, Moore-Clingenpeel M, Neely T, et al. Perception scores of siblings and parents of children with hypoplastic left heart syndrome. Congenit Heart Dis. 2018; 13(4): 528-32.

115. Mughal AR, Sadiq M, Hyder SN, Qureshi AU, SS AS, Khan MA, et al. Socioeconomic status and impact of treatment on families of children with congenital heart disease. J Coll Physicians Surg Pak. 2011; 21(7): 398-402.

116. Sharpe D, Rossiter L. Siblings of children with a chronic illness: a meta-analysis. J Pediatr Psychol. 2002; 27(8): 699-710.

117. Vermaes IP, van Susante AM, van Bakel HJ. Psychological functioning of siblings in families of children with chronic health conditions: a meta-analysis. J Pediatr Psychol. 2012; 37(2): 166-84.

118. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol. 2006; 48(8): 1527-37.

119. Fan H, Yu W, Zhang Q, Cao H, Li J, Wang J, et al. Depression after heart failure and risk of cardiovascular and all-cause mortality: a meta-analysis. Prev Med. 2014; 63: 36-42.

120. Junger J, Schellberg D, Muller-Tasch T, Raupp G, Zugck C, Haunstetter A, et al. Depression increasingly predicts mortality in the course of congestive heart failure. Eur J Heart Fail. 2005; 7(2): 261-7.

121. Sherwood A, Blumenthal JA, Hinderliter AL, Koch GG, Adams KF, Jr., Dupree CS, et al. Worsening depressive symptoms are associated with adverse clinical outcomes in patients with heart failure. J Am Coll Cardiol. 2011; 57(4): 418-23.

122. Sokoreli I, Pauws SC, Steyerberg EW, de Vries GJ, Riistama JM, Tesanovic A, et al. Prognostic value of psychosocial factors for first and recurrent hospitalizations and mortality in heart failure patients: insights from the OPERA-HF study. Eur J Heart Fail. 2018; 20(4): 689-96.

123. Angermann CE, Ertl G. Depression, Anxiety, and Cognitive Impairment : Comorbid Mental Health Disorders in Heart Failure. Curr Heart Fail Rep. 2018; 15(6): 398-410.

124. Celano CM, Villegas AC, Albanese AM, Gaggin HK, Huffman JC. Depression and Anxiety in Heart Failure: A Review. Harv Rev Psychiatry. 2018; 26(4): 175-84.

125. Vongmany J, Hickman LD, Lewis J, Newton PJ, Phillips JL. Anxiety in chronic heart failure and the risk of increased hospitalisations and mortality: A systematic review. Eur J Cardiovasc Nurs. 2016; 15(7): 478-85.

126. Glotzbach K, May L, Wray J. Health related quality of life and functional outcomes in pediatric cardiomyopathy. Progr Pediatr Cardiol. 2018; 48: 26-35.

127. den Boer SL, Baart SJ, van der Meulen MH, van Iperen GG, Backx AP, Ten Harkel AD, et al. Parent reports of health-related quality of life and heart failure severity score independently predict outcome in children with dilated cardiomyopathy. Cardiol Young. 2017; 27(6): 1194-202.

128. Wilmot I, Cephus CE, Cassedy A, Kudel I, Marino BS, Jefferies JL. Health-related quality of life in children with heart failure as perceived by children and parents. Cardiol Young. 2016; 26(5): 885-93.

129. Sleeper LA, Towbin JA, Colan SD, Hsu D, Orav EJ, Lemler MS, et al. Health-Related Quality of Life and Functional Status Are Associated with Cardiac Status and Clinical Outcome in Children with Cardiomyopathy. J Pediatr. 2016; 170: 173-80.

130. Wray J, Radley-Smith R. Cognitive and behavioral functioning of children listed for heart and/or lung transplantation. Am J Transplant. 2010; 10(11): 2527-35.

131. Menteer J, Beas VN, Chang JC, Reed K, Gold JI. Mood and health-related quality of life among pediatric patients with heart failure. Pediatr Cardiol. 2013; 34(2): 431-7.

132. Utens E, Callus E, Levert EM, Groote K, Casey F. Multidisciplinary family-centred psychosocial care for patients with CHD: consensus recommendations from the AEPC Psychosocial Working Group. Cardiol Young. 2018; 28(2): 192-8.

133. Landolt MA, Ystrom E, Stene-Larsen K, Holmstrom H, Vollrath ME. Exploring causal pathways of child behavior and maternal mental health in families with a child with congenital heart disease: a longitudinal study. Psychol Med. 2014; 44(16): 3421-33.

134. McCusker CG, Doherty NN, Molloy B, Rooney N, Mulholland C, Sands A, et al. A randomized controlled trial of interventions to promote adjustment in children with congenital heart disease entering school and their families. J Pediatr Psychol. 2012; 37(10): 1089-103.

135. Abda A, Bolduc ME, Tsimicalis A, Rennick J, Vatcher D, Brossard-Racine M. Psychosocial Outcomes of Children and Adolescents With Severe Congenital Heart Defect: A Systematic Review and Meta-Analysis. J Pediatr Psychol. 2018.

136. Ahn JA, Lee S, Choi JY. Comparison of coping strategy and disease knowledge in dyads of parents and their adolescent with congenital heart disease. J Cardiovasc Nurs. 2014; 29(6): 508-16.

137. Sood E, Karpyn A, Demianczyk AC, Ryan J, Delaplane EA, Neely T, et al. Mothers and Fathers Experience Stress of Congenital Heart Disease Differently: Recommendations for Pediatric Critical Care. Pediatr Crit Care Med. 2018; 19(7): 626-34.

138. Lawoko S, Soares JJ. Quality of life among parents of children with congenital heart disease, parents of children with other diseases and parents of healthy children. Qual Life Res. 2003; 12(6): 655-66.

139. Casey FA, Stewart M, McCusker CG, Morrison ML, Molloy B, Doherty N, et al. Examination of the physical and psychosocial determinants of health behaviour in 4-5-year-old children with congenital cardiac disease. Cardiol Young. 2010; 20(5): 532-7.

140. Drotar D. Psychological interventions in childhood chronic illness. Washington DC: American psychological Association; 2006.

141. Hirshfeld-Becker DR, Biederman J. Rationale and principles for early intervention with young children at risk for anxiety disorders. Clin Child Fam Psychol Rev. 2002; 5(3): 161-72.

142. Fox JK, Warner CM, Lerner AB, Ludwig K, Ryan JL, Colognori D, et al. Preventive intervention for anxious preschoolers and their parents: Strengthening early emotional development. Child Psychiatry and Human Development. 2012; .43(4): pp.

143. Connolly SD, Bernstein GA, Work Group on Quality I. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2007; 46(2): 267-83.

144. Thompson RJ, Jr., Gustafson KE, Hamlett KW, Spock A. Stress, coping, and family functioning in the psychological adjustment of mothers of children and adolescents with cystic fibrosis. J Pediatr Psychol. 1992; 17(5): 573-85.

145. Pahl KM, Barrett PM. The development of social-emotional competence in preschool-aged children: An introduction to the Fun FRIENDS program. Australian Journal of Guidance & Counselling. 2007; 17(1): 81-90.

146. Pahl KM, Barrett PM. Preventing anxiety and promoting social and emotional strength in preschool children: A universal evaluation of the Fun FRIENDS program. Adv Sch Ment Health Promot. 2010; 3(3): pp.

147. Anticich SAJ, Barrett PM, Silverman W, Lacherez P, Gillies R. The prevention of childhood anxiety and promotion of resilience among preschool-aged children: A universal school based trial. Adv Sch Ment Health Promot. 2013; 6(2).

148. Carlyle DA. With a little help from FUN FRIENDS young children can overcome anxiety. Community Pract. 2014; 87(8): 26-9.

149. Barrett P, Fisak B, Cooper M. The treatment of anxiety in young children: Results of an open trial of the Fun FRIENDS program. Behav Change. 2015; 32(4).

150. Fisak B, Gallegos-Guajardo J, Verreynne M, Barrett P. The results of a targeted open trial of the Fun FRIENDS combined with a concurrent parent-based intervention. Ment Health & Prev. 2018; 10: 35-41.

151. Shapiro F. Eye movement desensitization and reprocessing (EMDR): evaluation of controlled PTSD research. J Behav Ther Exp Psychiatry. 1996; 27(3): 209-18.

152. Organization WH. Guidelines for the management of conditions that are specifically related to stress. Geneva, Switzerland: World Health Organization; 2013.

153. de Roos C, van der Oord S, Zijlstra B, Lucassen S, Perrin S, Emmelkamp P, et al. EMDR versus cognitive behavioral writing therapy versus waitlist in pediatric PTSD following single-incident trauma: A multi-center randomized clinical trial. J Child Psychol Psychiatry. 2017; 58: 1219-28.

154. de Roos C, Greenwald R, den Hollander-Gijsman M, Noorthoorn E, van Buuren S, de Jongh A. A randomised comparison of cognitive behavioural therapy (CBT) and eye movement desensitisation and reprocessing (EMDR) in disaster-exposed children. Eur J Psychotraumatol. 2011; 2.

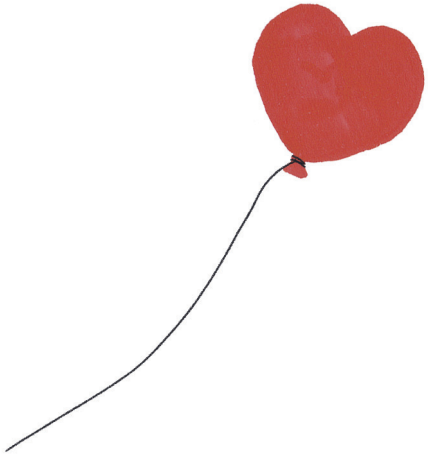
155. Chen YR, Hung KW, Tsai JC, Chu H, Chung MH, Chen SR, et al. Efficacy of eye-movement desensitization and reprocessing for patients with posttraumatic-stress disorder: a meta-analysis of randomized controlled trials. PLoS One. 2014; 9(8).

156. Shapiro F. The role of eye movement desensitization and reprocessing (EMDR) therapy in medicine: addressing the psychological and physical symptoms stemming from adverse life experiences. Perm J. 2014; 18(1): 71-7.

157. Bisson JI, Roberts NP, Andrew M, Cooper R, Lewis C. Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. Cochrane Database Syst Rev. 2013(12).

158. Rodenburg R, Benjamin A, de Roos C, Meijer AM, Stams GJ. Efficacy of EMDR in children: a meta-analysis. Clin Psychol Rev. 2009; 29(7): 599-606.

159. Moreno-Alcazar A, Treen D, Valiente-Gomez A, Sio-Eroles A, Perez V, Amann BL, et al. Efficacy of Eye Movement Desensitization and Reprocessing in Children and Adolescent with Post-traumatic Stress Disorder: A Meta-Analysis of Randomized Controlled Trials. Front Psychol. 2017; 8: 1750.



2

CHAPTER 2

Cognitive behavioral therapy for anxiety disorders in young children: a Dutch open trial of the Fun FRIENDS program

Malindi van der Mheen, Jeroen S. Legerstee, Gwendolyn C. Dieleman, Manon H.J. Hillegers, Elisabeth M.W.J. Utens

Behaviour Change, 2019, advance online publication

ABSTRACT

Anxiety disorders in young children are highly prevalent and increase the risk of social, school, and familial problems, and also of psychiatric disorders in adolescence and adulthood. Nevertheless, effective interventions for this age group are lacking. One of the few available interventions is the Fun FRIENDS program. We examined whether young children with anxiety disorders showed less anxiety after participating in Fun FRIENDS. Twenty-eight clinically anxious children (4-8 years old) participated in the cognitive behavioral Fun FRIENDS program. The program consists of 12 weekly 1.5-hour sessions and was provided in groups of 3 to 5 children. At pre-intervention and direct post-intervention, parents completed the Anxiety Disorders Interview Schedule for Children and Child Behavior Checklist. Clinically and statistically significant decreases were found in number of anxiety disorders, symptom interference, emotional and behavioral problems, internalizing problems, and anxiety problems. The decrease in anxious/depressed problems and externalizing problems was not significant. Furthermore, higher pre-intervention anxiety levels predicted more treatment progress, whereas sex and age did not. The Dutch version of Fun FRIENDS is promising in treating anxiety disorders in young children. Randomized controlled trials are needed to draw definite conclusions on the effectiveness of Fun FRIENDS in a clinical setting.

INTRODUCTION

Scientific interest in anxiety disorders in young children has increased in the past decade. Anxiety symptoms and diagnostic categories in young children resemble those in older children [1]. In young children, prevalence rates of anxiety disorders ranging from 9.4% [2] up to 22.2% [3] have been found. Unfortunately, anxiety disorders are often unrecognized in young children, because anxious children are considered to be shy, cooperative, and compliant [4]. If left unnoticed and untreated, this can have harmful consequences as early-onset anxiety disorders can become chronic [5, 6]. Research also shows that a diagnosis of an anxiety disorder in early childhood predicts anxiety and depression in adolescence and significantly increases the risk of having psychiatric disorders in adolescence and adulthood [5, 7-12]. Moreover, childhood anxiety disorders are associated with social [13], school [13, 14], and familial [15] problems. Anxiety disorders have a significant impact on societal costs due to poorer academic outcomes, financial dependence, and unemployment in adulthood [16, 17].

Considering these alarming outcomes, early intervention is urgently needed. Providing intervention at a young age has important advantages. First, anxious thoughts and behaviors may be easier to modify in younger children, as anxiety symptoms are likely to be less ingrained and neuroplasticity in young children is high [18]. Second, intervening early in the lifespan can minimize the impact of anxiety symptoms on the development and future of the child [18-21].

Despite the serious need for an evidence-based intervention for anxious young children, only a few studies have been conducted into interventions for this age group [21-23; for a complete overview, see 24]. An intervention that has been developed for 4- to 7-year-old children with anxiety disorders is the cognitive behavioral Fun FRIENDS program [25, 26]. The Fun FRIENDS program is an adaptation for young children of the evidence-based FRIENDS for Life program [27], which was based on the Coping Cat program [28]. The Fun FRIENDS program aims to increase children's emotional resilience, social-emotional skills, coping skills and to reduce emotional and behavioral problems. The program consists of 12 group sessions and is provided in a play-based manner, based on an experiential learning approach.

Until now, only two studies have examined the effectiveness of Fun FRIENDS delivered as a preventive program [22, 29]. In addition, three studies have studied

the outcomes of Fun FRIENDS delivered as a treatment program for young children with clinical internalizing symptoms or anxiety disorders [30-32].

Both prevention studies were randomized controlled trials in which Fun FRIENDS was delivered in a universal, classroom-based manner by psychology students or classroom teachers. In the first prevention study (N = 263, mean age = 4.56, SD = 0.51) [29], both the Fun FRIENDS intervention group and the waitlist control group showed comparable improvements on parent reports of anxiety, behavioral inhibition, and social-emotional strength. Regarding teacher reports, however, the Fun FRIENDS intervention group showed greater improvements than the waitlist control group as to behavioral inhibition and social-emotional strength, especially for girls. For ethical reasons, 12-month follow-up assessments were only completed for the intervention group. From pre-intervention to 12-month follow-up, the Fun FRIENDS intervention group showed improvements in anxiety, social-emotional strength, and, for girls, behavioral inhibition. In the second prevention study (N = 488, age range 4-7 years, mean age = 5.42, SD = 0.67) [22], children who had participated in Fun FRIENDS showed greater improvements as to behavioral and emotional strength and behavioral inhibition than children from the active control group (cognitive behavioral "You Can Do It" program [33]) and waitlist control group.

As to Fun FRIENDS as a treatment program, the first study consisted of a pilot study (N = 6, age range 4-7 years). This study suggested that Fun FRIENDS was effective in reducing anxiety of young children referred to a mental health service for anxiety symptoms [32]. The second treatment study was an open trial including young children (N = 31, age range 5-7, mean age = 5.68, SD = 0.54) who were diagnosed with one or more anxiety disorders [31]. From pre-intervention to immediate post-intervention, significant improvements as to anxiety symptoms, shyness, number of anxiety disorder diagnoses, and resilience were found. These results were maintained at 12-month follow-up. The third treatment study also was an open trial targeting young children (N = 178, age range 5-7, mean age = 5.27, SD = 0.93) with internalizing symptoms [30]. Their parents simultaneously received a resilience building program [34, 35]. For child outcomes, from pre-intervention to immediate post-intervention, significant reductions in internalizing symptoms and significant improvements in resilience were found.

Considering these promising outcomes, the Fun FRIENDS protocol was translated and adjusted for the Netherlands [36, 37]. The aim of the current study is to examine

whether young children with anxiety disorders show fewer anxiety symptoms after participating in the Dutch version of the Fun FRIENDS program, and to identify predictors of treatment progress. We thereby aim to add to the limited available knowledge concerning evidence-based treatment for young children with anxiety disorders and to contribute to the cross-cultural knowledge regarding this innovative cognitive behavioral program. We hypothesized that anxiety symptoms and the number of anxiety diagnoses would decrease after participating in Fun FRIENDS.

METHODS

Participants

Children who were 4-8 years old and met the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV) [38] diagnostic criteria for at least one anxiety disorder were eligible to participate in the Fun FRIENDS program. DSM-IV anxiety disorder criteria were assessed based on the parent version of the Anxiety Disorders Interview Schedule for Children (ADIS-C) [39]. All participants were referred to the Department of Child and Adolescent Psychiatry of the Erasmus Medical Center - Sophia Children's Hospital in Rotterdam between December 2008 and November 2013. Children with an IQ below 70 or a diagnosis of a posttraumatic stress disorder without a comorbid anxiety disorder were excluded from participation. In total, 28 children participated in the Fun FRIENDS program. Participant characteristics can be found in Table 1. As parental education is associated with persistence and severity of mental disorders [40], we have presented maternal education levels. Participants' primary anxiety disorder diagnoses are shown in Table 2 and all anxiety disorder diagnoses are shown in Table 3.

Table 1 Participant characteristics.

	N (%) or *M* (*SD*)		
Characteristic (*N*=28)	**Total sample (*N*=28)**	**ADIS-C completers (*N*=22)**	**CBCL completers (*N*=15)**
Sex			
Male	57.1%	13 (59.1%)	7 (46.7%)
Female	42.9%	9 (40.9%)	8 (53.3%)
Age			
Years	6.6 (1.1)	6.5 (1.0)	6.7 (1.0)
Nationality			
Dutch	20 (71.4%)	15 (68.2%)	13 (86.7%)
Unknown	8 (28.6%)	7 (31.8%)	2 (13.3%)
Total IQ	96.8 (15.7)	97.1 (17.6)	95.2 (9.6)
Maternal education level*			
Low	5 (17.9%)	5 (22.7%)	3 (20.0%)
Average	7 (25.0%)	4 (18.2%)	5 (33.3%)
High	6 (21.4%)	6 (27.3%)	4 (26.7%)
Unknown	10 (35.7%)	7 (31.8%)	3 (20.0%)

*Conform Dutch classification system [41].

Table 2 Participants' primary anxiety disorder diagnoses based on the ADIS-C at pre-intervention and post-intervention.

Primary anxiety disorder diagnosis	**Pre-intervention, *N* (%)**	**Post-intervention, *N* (%)**
Social anxiety disorder	8 (28.57%)	4 (14.29%)
Specific phobia	6 (21.43%)	4 (14.29%)
Separation anxiety disorder	4 (14.29%)	3 (10.71%)
Generalized anxiety disorder	3 (10.71%)	1 (3.57%)
Selective mutism	1 (3.57%)	2 (7.14%)
Obsessive compulsive disorder	2 (7.15%)	1 (3.57%)
No anxiety disorder	0 (0.00%)	11 (39.3%)
Unknown	4 (14.29%)	2 (7.14%)

Table 3 All anxiety disorder diagnoses based on the ADIS-C at pre-intervention and post-intervention.

Anxiety disorder diagnosis	Pre-intervention, *N*	Post-intervention, *N*
Social anxiety disorder	15	10
Specific phobia	10	7
Separation anxiety disorder	6	4
Generalized anxiety disorder	8	2
Selective mutism	4	2
Obsessive compulsive disorder	4	1
No anxiety disorder	0	11
Unknown	4	2

Procedure

This retrospective open trial study was conducted using a one-group pretest-posttest design. All parents were asked to complete assessments as part of the routine intake procedure (pre-intervention) and directly after the Fun FRIENDS intervention (post-intervention). As the Fun FRIENDS program was provided within the framework of regular treatment, assessments were completed as usual, and data were analyzed retrospectively, this study was not subject to the Dutch Medical Research Involving Human Subjects Act. The local research ethics committee was informed about the study and confirmed that full ethical approval of the study was not required. Participants were informed that collected data would be used anonymously in scientific research and that they could always opt out without any consequences for the treatment of their child.

Treatment

All children participated in the Dutch version of the Fun FRIENDS program [25, 42]. The program was delivered to seven consecutive treatment groups. Five groups consisted of 4 children, one group of 5 children, and one group of 3 children (n = 28). The children received 12 weekly 1.5-hour sessions. On average, the program was delivered over a time period of 3.5 months. All sessions were led by two licensed, experienced psychologists. One of them received training from the developer of the Fun FRIENDS program. At each session, a master's student in psychology was present to make observations, take notes, and assist the psychologists. The content of each session is described in Table 4. During the last 15 minutes of each session, the master's student observed the children during free play while in a separate room, the psychologists gave the group of parents further information about the

home assignments and the exercises performed during the session. The last child session was a booster session in which parents were present and actively involved. All families received a Fun FRIENDS workbook [43, 44], which contained home assignments and additional information about the program.

Measures

Anxiety Disorders Interview Schedule for Children (ADIS-C)

The ADIS-C [39, 45] is a semi-structured interview that was used to assess the presence and severity of DSM-IV anxiety disorders in children and adolescents. The ADIS-C was conducted with parents to assess the following DSM-IV diagnoses: selective mutism, generalized anxiety disorder, social phobia, specific phobia, separation anxiety disorder, panic disorder, agoraphobia, obsessive-compulsive disorder, and posttraumatic stress disorder. For each diagnosis confirmed based on the interview, the parent was asked to rate to what extent the symptoms interfered with the child's daily life on a 9-point scale (i.e., 0-8, higher scores indicating a higher level of interference). Subsequently, the interviewer rated the level of interference on the same 9-point scale, yielding the Clinician Severity Rating (CSR). A CSR of 4 or higher indicates that a DSM-IV diagnosis can be confirmed and assigned. Strong interrater reliability, retest reliability, and concurrent validity have been found for the ADIS-C C [39, 46]. Pre-intervention and post-intervention interviews were conducted by a different interviewer. All ADIS-C interviews were administered by trained psychologists or trained master's students in psychology. To ensure that all interviewers conducted reliable and valid scoring, the master's students were thoroughly trained by observing live and videotaped interviews. Moreover, they received regular supervision regarding their ADIS-C interviews by their supervising experienced clinical psychologist or psychiatrist and all ADIS-C interviews were reviewed and discussed in multidisciplinary meetings.

Child Behavior Checklist (CBCL)

The CBCL 1½-5 (100 items; for 5-year-olds) [47] and CBCL/6-18 (120 items; for 6- to 8-year-olds) [47] were completed by parents to assess emotional and behavioral problems in children before and after the intervention. Response categories range from 0 to 2, higher scores indicating more problems. The CBCL yields two broadband scales of externalizing and internalizing behaviors and an overall total score. Furthermore, both the CBCL 1½-5 and the CBCL/6-18 encompass the Anxious/Depressed syndrome scale and the DSM-oriented Anxiety Problems scale. Adequate psychometric properties have been found [48].

Statistical analysis

First, differences in baseline characteristics between children with complete assessments and children with incomplete assessments were examined using independent samples t-tests for continuous data and Chi-squared tests or Fisher's exact tests for categorical data.

Second, for the ADIS-C, a Wilcoxon signed-rank test was computed to assess the difference between the number of anxiety disorders at pre-intervention and post-intervention. The difference between average pre-intervention and post-intervention interference scores rated by parents was examined through a paired samples t-test. Unfortunately, too many CSRs were missing at pre-intervention and post-intervention to complete statistically warranted reliable analyses on these data. CSRs were missing due to the retrospective design of the study. As all assessments were conducted as part of regular clinical care, data was not systematically entered into a scientific database. Moreover, changes in digital medical file systems caused logistical difficulties in retrieving a sufficient number of CSRs.

Third, CBCL scores were standardized using t-scores as two different versions were used (i.e., CBCL 1½-5 and CBCL/6-18). Differences between pre-intervention and post-intervention CBCL scores were examined using paired samples t-tests.

Finally, it was examined whether sex, age, or pre-intervention anxiety scores independently predicted treatment progress. Treatment progress was calculated by subtracting post-intervention anxiety problem scores on the CBCL from pre-intervention anxiety problem scores (primary outcome). To examine whether children's sex predicted treatment progress, an independent samples t-test was conducted. To examine whether children's age at the start of participation in the Fun FRIENDS program predicted treatment progress, a simple linear regression analysis was performed. Another simple linear regression analysis was performed to examine whether pre-intervention scores on the anxiety problems subscale of the CBCL predicted treatment progress.

Table 4 Outline of Fun FRIENDS sessions

Session	Content of session
Session 1	· Introduction to the group. · Development of a positive sense of identity. · Social skills promotion, 'being brave' (e.g., using a brave voice, making eye contact, smiling). · Acceptance of differences and similarities between people.
Session 2	**F**: Feelings · Identification and recognition of various emotions. · Understanding feelings in self and others. · Empathy building, awareness of own emotional responses, and emotion regulation.
Session 3	**F**: Feelings (continued) · Coping with emotions; helpful (thumbs up) and unhelpful (thumbs down) behaviors to regulate feelings. · Children think of ways to help others when they experience certain emotions. · The link between emotions and behavior is discussed.
Session 4	**R**: Remember to relax · Identification of physiological arousal ('body clues') related to anxiety. · Teaching of relaxation strategies to feel more calm and brave (e.g., diaphragmatic breathing, progressive muscle relaxation, visualization).
Session 5	**I**: I can try my best! · Introduction of cognitive components of the program. · Identification and awareness of inner thoughts (self-talk), unhelpful (red) and helpful (green) thoughts. To explain red and green thoughts, the analogy of a traffic light is used. When we have happy green thoughts, we want to go! When we have unhappy red thoughts, we want to stop!
Session 6	**I**: I can try my best! (continued) · Challenging 'red' thoughts and changing unhelpful 'red' thoughts into helpful 'green' thoughts.
Session 7	**E**: Encourage · The concept of coping step plans is explained. Children are taught how to try new things by breaking tasks down into small steps (graded exposure anxiety hierarchies). Step plans are also explained to parents. · Focus on friendship skills (e.g., sharing, helping, smiling).
Session 8	**N**: Nurture · The idea and importance of people who help us achieve our goals (support teams) in different environments is discussed.

Table 4 Continued

Session	Content of session
Session 9	**D**: Don't forget to be brave · Support teams continued. · Planning for difficult (future) situations.
Session 10	**S**: Stay smiling · Party session: celebration of success in completing the program. Children dress up as their favorite brave person and receive their Fun FRIENDS certificate. Parents are also present.
Session 11 & 12	Booster sessions: review learnt strategies and prepare for future challenges.

RESULTS

Mean scores are presented in Table 5. One child missed 6 out of 12 sessions due to logistical reasons, but was included in the analyses according to the intention-to-treat principle. For two children, both the ADIS-C and the CBCL were not fully completed. Therefore, these children were excluded from all analyses.

Table 5 Mean scores for outcome variables and statistical comparisons between pre-intervention and post-intervention.

	Mean (SD)			
Measure	**Pre-intervention**	**Post-intervention**	**p-value**	**Effect size**
ADIS-C (*N* = 22)				
Number of anxiety disorders [a]	2.09 (1.07)	1.00 (1.16)	.002	0.65[c]
Interference score rated by parents [b]	1.22 (0.77)	0.63 (0.78)	.003	0.76[d]
CBCL t-scores‡ (*N* = 15)				
Total problem score [b]	60.20 (9.70)	56.60 (11.25)	.032	0.34[d]
Internalizing problems [b]	62.27 (11.70)	58.87 (11.14)	.036	0.30[d]
Externalizing problems [b]	54.07 (9.79)	52.47 (10.98)	.321	0.15[d]
Anxiety problems [b]	66.13 (8.99)	62.07 (7.97)	.048	0.48[d]
Anxious/depressed [b]	64.60 (9.85)	61.33 (8.20)	.094	0.36[d]

‡ Mother-report.
a. Wilcoxon signed-rank test.
b. Paired samples t-test.
c. $r = z / \sqrt{N}$
d. Cohen's *d*.

ADIS-C

Parents of 22 children completed the ADIS-C at both pre-intervention and post-intervention. Children with complete ADIS-C assessments did not differ from children with incomplete ADIS-C assessments in terms of age, sex, total IQ, and maternal education level (all $p \geq .08$).

The mean number of anxiety disorders decreased significantly from pre-intervention ($M = 2.09$, $SD = 1.07$) to post-intervention ($M = 1.00$, $SD = 1.16$), $z = -3.04$, $p = .002$. The effect size was $r = 0.65$, indicating a large to very large effect [49]. The average interference score rated by parents also significantly decreased from pre-intervention ($M = 1.22$, $SD = 0.77$) to post-intervention ($M = 0.63$, $SD = 0.78$), $t(22) = 3.34$, $p = .003$. The effect size was $d = 0.76$, indicating a large effect [49].

CBCL

Unfortunately, the number of CBCLs completed by fathers was too small to analyze. Therefore, only CBCL data reported by mothers was analyzed. Mothers of 15 children completed the CBCL at both pre- and post-intervention. Children with complete CBCL assessments did not differ from children with incomplete CBCL assessments in terms of age, sex, total IQ, and maternal education level (all $p > .27$).

A significant decrease in CBCL total problem scores was found, $t(14) = 2.38$, $p = .032$, $d = 0.34$, which indicates that overall emotional and behavioral problems decreased from pre-intervention to post-intervention. A significant decrease was also found for internalizing problems, $t(14) = 2.32$, $p = .036$, $d = 0.30$, and anxiety problems, $t(14) = 2.17$, $p = .048$, $d = 0.48$. The effect sizes indicate small to medium effects [49]. The observed decrease in scores of the anxious/depressed subscale was not significant, $p = .094$, $d = 0.36$. The decrease in externalizing problems was also not significant, $p = .321$, $d = 0.15$.

Predictors of treatment progress

Treatment progress was defined as the difference between pre-intervention and post-intervention CBCL anxiety problems score (primary outcome). A positive score indicates treatment progress (i.e., a lower anxiety problems score at post-intervention than at pre-intervention).

Sex and age

Treatment progress of boys (mean Δ = 3.00, SD = 7.94) and girls (mean Δ = 5.00, SD = 7.05) did not significantly differ, p = .614, d = 0.27, indicating that sex does not predict treatment progress. Moreover, children's age at start of participation in Fun FRIENDS did not significantly predict treatment progress, p = .73.

Anxiety problems at pre-intervention

The level of pre-intervention anxiety problems did significantly predict treatment progress, β = .537, F(1) = 5.27, p = .04, R^2 = .29. This indicates that a higher pre-intervention anxiety problems score predicts more treatment progress (demonstrated by a larger positive difference between pre-intervention and post-intervention anxiety problems).

DISCUSSION

The current study examined whether anxiety in young children with anxiety disorders decreases after participating in the cognitive behavioral Fun FRIENDS program. As expected, we found significant decreases in the number of anxiety disorder diagnoses and symptom interference with young children's daily lives as reported by parents. Moreover, we found significant decreases in emotional and behavioral problems, internalizing problems, and anxiety problems. These results suggest that the Dutch version of the Fun FRIENDS program is promising in treating anxiety disorders in young children in a clinical setting, which is in line with previous findings [31, 32]. Children with higher levels of pre-intervention anxiety problems seemed to benefit most from the Fun FRIENDS program, which is also in line with previous findings [31]. Sex and age did not predict treatment progress.

The decrease in anxious/depressed symptoms, however, was not significant. This might be surprising, as the Fun FRIENDS program specifically targets issues such as anxiety and depression [26]. Moreover, previous studies have shown that the FRIENDS for Life program (for children aged 8-12 years), on which the Fun FRIENDS program was based, is effective in reducing both anxiety and depressive symptoms (e.g., 50-52]. The difference in results may be explained by the used outcome measures. To measure depressive symptoms, previous studies used the Children's Depression Inventory (CDI) [53] and the Revised Child Anxiety and Depression Scale (RCADS) [54], whereas the current study used the CBCL. Moreover, the children who participated in the current study received treatment because they were diagnosed with anxiety disorders. Based on pre-intervention ADIS-C scores,

no children were diagnosed with a depressive disorder at baseline. It should also be noted that, considering the trend towards significance, the decrease in anxious/depressive symptoms may have reached the level of significance if the sample size had been larger.

It is not surprising that externalizing problems did not significantly decrease after participating in the Fun FRIENDS program because Fun FRIENDS mainly targets internalizing problems [26]. In addition, overall, participants' pre-intervention externalizing problem scores were relatively low and not the main target of treatment. Therefore, a significant decrease in externalizing problems might not have been likely.

This study has several strengths. First, it adds to the limited evidence-based knowledge body concerning treatment for young children with clinical levels of anxiety. Second, this is the first European study examining the Fun FRIENDS program. It is important to cross-validate findings across countries using the same validated assessment instruments and protocols. This enables us to draw more robust conclusions as to outcomes after participating in the Fun FRIENDS program. Third, the senior psychologist providing the Fun FRIENDS program was trained by the program developer; and, fourth, treatment was fully manualized and standardized.

However, although promising, the results of the current study should be interpreted with caution as the study did not include a control group, which limits the internal validity [55]. In this study, internal validity refers to whether the decline in symptoms can be attributed to participating in the Fun FRIENDS program. Without the use of a control group, it is not possible to draw definite conclusions as to the effectiveness of an intervention, because other influences on the outcome cannot be ruled out. For example, the decline in symptoms may also be influenced by maturation (i.e., naturally occurring changes over time) or regression to the mean (i.e., the tendency to score less extremely on a posttest assessment than on a pretest assessment). In the future, randomized controlled trials with larger groups of participants should be conducted in order to draw definite conclusions as to the effectiveness of the Fun FRIENDS program. It would also be useful to include a long term follow-up assessment to examine whether the obtained results remain over a longer period of time.

Moreover, to optimize treatment for young children with anxiety disorders, future research should focus on which elements of the Fun FRIENDS program are most useful. Future research could also consider the format in which the intervention is delivered. A randomized controlled trial has shown that the FRIENDS for Life program [27] (translated by [42]) is equally effective in diminishing anxiety through individual treatment as through group treatment [56]. Whether this also holds true for the Fun FRIENDS program should be examined in future research. The psychologists, parents, and children involved in the current study considered the group format to be beneficial. The group format seemed to enable children to learn from each other and to encourage each other in learning the cognitive behavioral techniques. However, when delivering an intervention in a group format, children may drop out due to different issues (e.g., change in parents' working schedule), which may also have a negative influence on the rest of the group. For this reason, prior to participating in the program, we asked parents to fully commit to the treatment.

In conclusion, the Fun FRIENDS program is one of the very few cognitive behavioral treatment programs for young children with anxiety disorders. The current study shows promising results as to the outcomes after participating in the Fun FRIENDS program. To determine the effectiveness of the program in a clinical setting, randomized controlled trials with longer follow-up periods are needed.

ACKNOWLEDGEMENTS

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

DECLARATION OF INTEREST

The authors declare that they have no conflict of interest. EU translated the FRIENDS for Life and Fun FRIENDS manuals to Dutch but does not receive remuneration for this.

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

REFERENCES

1. Mian ND, Godoy L, Briggs-Gowan MJ, Carter AS. Patterns of anxiety symptoms in toddlers and preschool-age children: evidence of early differentiation. J Anxiety Disord. 2012; 26(1): 102-10.
2. Egger HL, Angold A. Common emotional and behavioral disorders in preschool children: presentation, nosology, and epidemiology. J Child Psychol Psychiatry. 2006; 47(3-4): 313-37.
3. Paulus FW, Backes A, Sander CS, Weber M, von Gontard A. Anxiety disorders and behavioral inhibition in preschool children: a population-based study. Child Psychiatry Hum Dev. 2015; 46(1): 150-7.
4. Albano AM, Chorpita BF, Barlow DH. Child psychopathology. In: Mash EJ, Barkley RA, editors. Childhood anxiety disorders. New York: Guilford Press; 2003. p. 279-329.
5. Essau CA, Lewinsohn PM, Lim JX, Ho MR, Rohde P. Incidence, recurrence and comorbidity of anxiety disorders in four major developmental stages. J Affect Disord. 2018; 228: 248-53.
6. Essau CA, Lewinsohn PM, Olaya B, Seeley JR. Anxiety disorders in adolescents and psychosocial outcomes at age 30. J Affect Disord. 2014; 163: 125-32.
7. Copeland WE, Adair CE, Smetanin P, Stiff D, Briante C, Colman I, et al. Diagnostic transitions from childhood to adolescence to early adulthood. J Child Psychol Psychiatry. 2013; 54(7): 791-9.
8. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. Arch Gen Psychiatry. 2003; 60(8): 837-44.
9. Bienvenu OJ, Ginsburg GS. Prevention of anxiety disorders. Int Rev Psychiatry. 2007; 19(6): 647-54.
10. Bittner A, Egger HL, Erkanli A, Jane Costello E, Foley DL, Angold A. What do childhood anxiety disorders predict? J Child Psychol Psychiatry. 2007; 48(12): 1174-83.
11. Copeland WE, Shanahan L, Costello J, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. Arch Gen Psychiatry. 2009; 66(7).
12. Moffitt TE, Caspi A, Harrington H, Milne BJ, Melchior M, Goldberg D, et al. Generalized anxiety disorder and depression: childhood risk factors in a birth cohort followed to age 32. Psychol Med. 2007; 37(3): 441-52.
13. de Lijster JM, Dieleman GC, Utens E, Dierckx B, Wierenga M, Verhulst FC, et al. Social and academic functioning in adolescents with anxiety disorders: A systematic review. J Affect Disord. 2018; 230: 108-17.
14. Mychailyszyn MP, Mendez JL, Kendall PC. School functioning in youth with and without anxiety disorders: Comparisons by diagnosis and comorbidity. School Psych Rev. 2010; 39(1).

15. Towe-Goodman NR, Franz L, Copeland W, Angold A, Egger H. Perceived family impact of preschool anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2014; 53(4): 437-46.

16. Bodden DH, Dirksen CD, Bogels SM. Societal burden of clinically anxious youth referred for treatment: a cost-of-illness study. J Abnorm Child Psychol. 2008; 36(4): 487-97.

17. Barrett PM, Cooper M, Teoh ABH. When Time is of the Essence: A Rationale for 'Earlier' Early Intervention. J Psychol Abnorm Child. 2014; 3(133).

18. Hirshfeld-Becker DR, Biederman J. Rationale and principles for early intervention with young children at risk for anxiety disorders. Clin Child Fam Psychol Rev. 2002; 5(3): 161-72.

19. Donovan CL, March S. Online CBT for preschool anxiety disorders: a randomised control trial. Behav Res Ther. 2014; 58: 24-35.

20. Connolly SD, Bernstein GA, Work Group on Quality I. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2007; 46(2): 267-83.

21. Fox JK, Warner CM, Lerner AB, Ludwig K, Ryan JL, Colognori D, et al. Preventive intervention for anxious preschoolers and their parents: Strengthening early emotional development. Child Psychiatry Hum Dev. 2012; 43(4).

22. Anticich SAJ, Barrett PM, Silverman W, Lacherez P, Gillies R. The prevention of childhood anxiety and promotion of resilience among preschool-aged children: A universal school based trial. Adv Sch Ment Health Promot. 2013; 6(2).

23. von Klitzing K, Dohnert M, Kroll M, Grube M. Mental Disorders in Early Childhood. Dtsch Arztebl Int. 2015; 112(21-22): 375-86.

24. Fisak B, Barrett P. Anxiety in preschool children: Assessment, treatment, and prevention. New York, NY: Routledge; 2019.

25. Barrett PM. Fun FRIENDS: The teaching and training manual for group leaders. Brisbane: Fun FRIENDS Publishing; 2007.

26. Pahl KM, Barrett PM. The development of social-emotional competence in preschool-aged children: An introduction to the Fun FRIENDS program. J Psychol Couns Sch. 2007; 17(1): 81-90.

27. Barrett PM, Turner C. Friends for children: Group leader's manual. Bowen Hills, Australia: Australian Academic Press; 2000.

28. Kendall PC. Treating anxiety disorders in children: results of a randomized clinical trial. J Consult Clin Psychol. 1994; 62(1): 100-10.

29. Pahl KM, Barrett PM. Preventing anxiety and promoting social and emotional strength in preschool children: A universal evaluation of the Fun FRIENDS program. Adv Sch Ment Health Promot. 2010; 3(3).

30. Fisak B, Gallegos-Guarjardo J, Verreynne M, Barrett P. The results of a targeted open trial of the Fun FRIENDS combined with a concurrent parent-based intervention. Ment Health Prev. 2018; 10: 35-41.

31. Barrett P, Fisak B, Cooper M. The treatment of anxiety in young children: Results of an open trial of the Fun FRIENDS program. Behav Change. 2015; 32(4).

32. Carlyle DA. With a little help from FUN FRIENDS young children can overcome anxiety. Community Pract. 2014; 87(8): 26-9.

33. Ashdown DM, Bernard ME. Can explicit instruction in social and emotional learning skills benefit the social-emotional development, well-being, and academic achievement of young children? Early Child Educ J. 2011; 39: 397-405.

34. Barrett PM. Strong Not Tough Adult Program: Resilience Throughout Life (2nd ed.). Brisbane, Australia: Pathways Health and Research Centre; 2012.

35. Barrett, P. M. (2012). Strong Not Tough Adult Program: Resilience Throughout Life: Guidelines for Facilitators (2nd ed.). Brisbane, Australia: Pathways Health and Research Centre; 2012.

36. Utens EMWJ. FIJN: VRIENDEN! Handleiding voor ouders om emotionele veerkracht door middel van spel op te bouwen bij 4 tot en met 7 jarigen. Rotterdam: Erasmus MC - Sophia Kinderziekenhuis; 2011.

37. Utens EMWJ. FIJN: VRIENDEN! Handleiding voor trainers om emotionele veerkracht door middel van spel op te bouwen bij 4 tot en met 7 jarigen. Rotterdam: Erasmus MC - Sophia; 2011.

38. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed.). Washington, DC: Author; 1994.

39. Silverman WK, Saavedra LM, Pina AA. Test-retest reliability of anxiety symptoms and diagnoses with the Anxiety Disorders Interview Schedule for DSM-IV: child and parent versions. J Am Acad Child Adolesc Psychiatry. 2001; 40(8): 937-44.

40. McLaughlin KA, Breslau J, Green JG, Lakoma MD, Sampson NA, Zaslavsky AM, Kessler RC. Childhood socio-economic status and the onset, persistence, and severity of DSM-IV mental disorders in a US national sample. Soc Sci Med. 2011; 73(7): 1088-96.

41. Centraal Bureau voor de Statistiek (CBS; Statistics Netherlands). Standaard onderwijsindeling: Editie 2016/'17. Den Haag/Heerlen; 2017.

42. Utens EMWJ, de Nijs P, Ferdinand RF. FRIENDS for children – manual for group leaders (Dutch translation). Rotterdam, the Netherlands: Department of Child and Adolescent Psychiatry Erasmus Medical Centre - Sophia Children's Hospital; 2001.

43. Barrett PM. FUN FRIENDS: a parent's guide for building resilience in 4 to 7-year-old children through play. Brisbane: Fun Friends Publishing; 2007.

44. Utens EMWJ. FIJN: VRIENDEN! Handleiding voor ouders om emotionele veerkracht door middel van spel op te bouwen bij 4- tot en met 7-jarigen. Rotterdam: Erasmus MC - Sophia Kinderziekenhuis; 2011.

45. Siebelink BM, Treffers PDA. Anxiety Disorder Interview Schedule for DSM-IV Child Version/Dutch Translation. Lisse: SWETS Test Publishers; 2001.

46. Lyneham HJ, Abbott MJ, Rapee RM. Interrater reliability of the Anxiety Disorders Interview Schedule for DSM-IV: child and parent version. J Am Acad Child Adolesc Psychiatry. 2007; 46(6): 731-6.

47. Achenbach TM, Rescorla LA. Manual for the ASEBA school-age forms & profiles. Burlington, Vermont: University of Vermont, Research Center for Children, Youth, & Families; 2001.

48. Achenbach TM, Becker A, Dopfner M, Heiervang E, Roessner V, Steinhausen HC, et al. Multicultural assessment of child and adolescent psychopathology with ASEBA and SDQ instruments: research findings, applications, and future directions. J Child Psychol Psychiatry. 2008; 49(3): 251-75.

49. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Second edition ed. New York: Lawrence Erlbaum Associates; 1988.

50. Ahlen J, Breitholtz E, Barrett PM, Gallegos J. School-based prevention of anxiety and depression: a pilot study in Sweden. Adv Sch Ment Health Promot. 2012; 5(4): 246-57.

51. World Health Organization (WHO). Prevention of mental disorders: Effective interventions and policy options. Geneva, Switzerland; 2004.

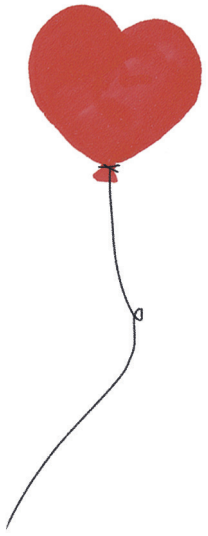
52. Essau CA, Conradt J, Sasagawa S, Ollendick TH. Prevention of anxiety symptoms in children: results from a universal school-based trial. Behav Ther. 2012; 43(2): 450-64.

53. Kovacs M. The Children's Depression Inventory (CDI). Psychopharmacol Bull. 1985; 21: 995-8.

54. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. Behav Res Ther. 2000; 38: 835-55.

55. Shadish W, Cook TD, Campbell DT. Experimental and quasi-experimental designs for generalized causal inference. Boston, MA: Houghton Mifflin; 2002.

56. Liber JM, Van Widenfelt BM, Utens EMWJ, Ferdinand RF, Van der Leeden AJM, Van Gastel W, et al. No differences between group versus individual treatment of childhood anxiety disorders in a randomised clinical trial. J Child Psychol Psychiatry. 2008; 49(8).



3

CHAPTER 3

The CHIP-Family study to improve the psychosocial wellbeing of young children with congenital heart disease and their families: design of a randomized controlled trial

Malindi van der Mheen, Ingrid M. van Beynum, Karolijn Dulfer, Jan van der Ende, Eugène van Galen, Jorieke Duvekot, Lisette E. Rots, Tabitha P.L. van den Adel, Ad J.J.C. Bogers, Christopher G. McCusker, Frank A. Casey, Willem A. Helbing, Elisabeth M.W.J. Utens

BMC Pediatrics, 2018, 18:230

ABSTRACT

Background. Children with congenital heart disease (CHD) are at increased risk for behavioral, emotional, and cognitive problems. They often have reduced exercise capacity and participate less in sports, which is associated with a lower quality of life. Starting school may present more challenges for children with CHD and their families than for families with healthy children. Moreover, parents of children with CHD are at risk for psychosocial problems. Therefore, a family-centered psychosocial intervention for children with CHD when starting school is needed. Until now, the 'Congenital Heart Disease Intervention Program (CHIP) – School' is the only evidence-based intervention in this field. However, CHIP-School targeted parents only and resulted in non-significant, though positive, effects as to child psychosocial wellbeing. Hence, we expanded CHIP by adding a specific child module and including siblings, creating the CHIP-Family intervention. The CHIP-Family study aims to (1) test the effects of CHIP-Family on parental mental health and psychosocial wellbeing of CHD-children and to (2) identify baseline psychosocial and medical predictors for the effectiveness of CHIP-Family.

Methods. We will conduct a single-blinded randomized controlled trial comparing the effects of CHIP-Family with care as usual (no psychosocial intervention). Children with CHD (4-7 years old) who are starting or attending kindergarten or primary school (first or second year) at the time of first assessment and their families are eligible. CHIP-Family consists of a separate one-day workshop for parents and children. The child workshop consists of psychological exercises based on the evidence-based cognitive behavioral therapy Fun FRIENDS protocol and sports exercises. The parent workshop focuses on problem prevention therapy, psychoeducation, general parenting skills, skills specific to parenting a child with CHD, and medical issues. Approximately four weeks after the workshop, parents receive an individual follow-up session. The baseline (T1) and follow-up assessment (T2 = 6 months after T1) consist of online questionnaires filled out by the child, parents, and teacher (T2 only). Primary outcome measures are the CBCL for children and the SCL-90-R for parents.

Discussion. This trial aims to test the effects of an early family-centered psychosocial intervention to meet the compelling need of young children with CHD and their families to prevent (further) problems. If CHIP-Family proves to be effective, it should be structurally implemented in standard care.

INTRODUCTION

Children with congenital heart disease (CHD) are at elevated risk for behavioral, emotional, and cognitive problems in childhood [1, 2], adolescence, and adulthood [3]. Previous cohort studies from our research group have indicated that CHD-children are two times more likely to develop psychopathology than healthy children (16-27% versus 10% in the general population) - irrespective of the type of cardiac defect [4, 5]. Especially internalizing behavior problems, problems with social contacts, and reduced quality of life have been reported [6]. Moreover, neuropsychological problems and intellectual impairments are well known in these children [7, 8] and elevated percentages of CHD-children attending special education (24% versus 4% in norm) have been reported [3]. The most common morbidity affecting the quality of life in school-aged children with CHD is the combination of behavioral/emotional problems, developmental delay, and school difficulties [9]. Such problems can have long-term consequences: two long-term studies have shown that adults with CHD overall had a lower occupational and educational status compared with the general population [10, 11]. Furthermore, children with CHD often have reduced exercise capacity and participate less in exercise and sports, which has been associated with a lower quality of life [13]. It has been shown that participation in an exercise program improves quality of life of children with CHD [12].

In addition, parental factors play a crucial role in children's psychosocial wellbeing [2, 14-16]. Maternal mental health and worry have appeared to be more important predictors of psychosocial wellbeing of children with CHD than illness severity [2, 17, 18]. Unfortunately, parents of children with CHD are also at risk for psychosocial problems themselves (e.g. anxiety, depression; one year prevalence 7-22%) [19].

Considering the above and the fact that milestones such as starting kindergarten and primary school present more challenges for children with CHD and their parents than for families with healthy children [20], a family-based psychosocial intervention tailored to their needs when starting school is required [19, 21, 22]. This need has also been expressed by parents and patients [21, 23]. Through such an intervention, psychosocial problems of children with CHD and their parents may be recognized, reduced or prevented. In addition, school functioning, emotional resilience, and sports participation of these children can be improved [21, 24]. Until now, the only evidence-based intervention in this field is the Congenital Heart Disease Intervention Program (CHIP) – School [2]. The CHIP-School study aimed to

promote psychosocial wellbeing of preschoolers with CHD indirectly by providing an intervention for their parents. CHIP-School resulted in significant gains in maternal mental health, reduced perceived strain on the family, and less school absence of the child. As to child psychosocial wellbeing, only a non-significant, though positive, trend was found [2].

A limitation of CHIP-School was that a separate child module was not included. Therefore, in collaboration with the original authors of the previous CHIP intervention, we have translated, extended and modified CHIP, by adding a tailored child module for CHD-children and their siblings. The child module includes evidence-based cognitive behavioral exercises [26] and sports exercises. The newly developed CHIP-Family is a psychosocial intervention for 4- to 7-year-old children who have undergone at least one medical intervention for CHD and are starting or attending kindergarten or primary school (first or second year) and their families.

The aim of this study is (1) to test the effects of CHIP-Family on parental mental health and psychosocial wellbeing of CHD-children who are starting or attending kindergarten or primary school and to (2) identify baseline psychosocial and medical predictors for the effectiveness of CHIP-Family.

METHODS

This study is a single-center, single-blinded randomized controlled trial (RCT) comparing the effects of the CHIP-Family intervention with care as usual (CAU; regular medical treatment) on mental health of parents and psychosocial wellbeing of young children with CHD. This RCT is designed according to the CONSORT guidelines [27].

Inclusion and exclusion criteria

Over a one-year period (September 2016 – September 2017) children and their families living in the Netherlands will be recruited. Eligible are all children who (1) underwent at least one invasive procedure (catheter intervention or surgery) for CHD and (2) are starting or attending kindergarten or primary school (first or second year) at the time of first assessment (as the children are approximately 4-7 years old). Exclusion criteria are: (1) child's intellectual impairment (IQ < 70) as ascertained by previous standardized assessment or diagnosed by a clinician, (2) insufficient mastery of the Dutch language, and (3) prematurely born children

(gestational age at birth < 37 weeks) with no other CHD than a patent ductus arteriosus.

Recruitment and procedure

Parents of 4- to 7-year-old children who receive treatment at the department of pediatric cardiology of the Erasmus Medical Center – Sophia Children's Hospital and eligible members of the Dutch Patient Association for Congenital Heart Disease whose children receive treatment in a cardiac centre in the Netherlands will receive an information leaflet explaining the purpose and procedures of the study. Before inclusion, parents will receive a verbal explanation of the trial. After obtaining written parental informed consent, patients are randomly allocated to the CHIP-Family intervention or CAU group. To avoid a delay of more than 1 month between baseline assessment and the intervention, patients are randomized prior to the baseline assessment. Patients are allocated to the CHIP-Family intervention or CAU group by means of block randomization, performed by an independent researcher. Randomization will be stratified by CHD severity (limited to no residual heart defects or moderate to severe residual heart defects [after medical intervention]; see Table 1) and school year (kindergarten or primary school). To avoid bias, the researcher performing the assessments and analyses will be blinded. Considering the nature of the CHIP-Family intervention, it is not possible to blind the participants and the health care professionals providing the intervention.

Table 1 Stratification factor "CHD severity".

Type 1 Limited to no residual heart defects	**Type 2** Moderate to severe residual heart defects
Atrial Septal Defect (ASD)	ALCAPA (Anomalous Left Coronary Artery from the Pulmonary Artery)
Patent Ductus Arteriosus	Aortic Valve Stenosis
Pulmonary valve stenosis	Atrioventricular Septal Defect (AVSD)
Total Anomalous Pulmonary Venous Connection	Coarctation of the Aorta
Ventricular Septal Defect (VSD)	Complex Biventricular (e.g. Truncus Arteriosus, aortic arch defects)
	Double Inlet Ventricle – Fontan circulation
	Ebstein's Anomaly
	Subvalvular Aortic Stenosis
	Tetralogy of Fallot (TOF)
	TOF with MAPCA (Main Aorta to Pulmonary Connecting Artery)
	Transposition of the Great Arteries

Intervention

CHIP-Family consists of a parent module and a child module. Parents and children participate in a separate, but simultaneously given, 6-hour group workshop. An overview of the content of the workshops is given in Table 2. Over the course of a 11-month period (Nov. 2016 – Sept. 2017) 11 workshops will be given to 3 to 5 families per workshop.

Table 2 Outline of the CHIP-Family workshops.

Parent workshop	
Health care professional(s)	**Content**
Psychologists	· Problem prevention therapy [50]. A DO ACT acronym is applied: **D**efine problem and turn into a specific goal; **O**ption brainstorm; **A**ssess pros and cons of various options; **C**hoose a strategy; **T**ake action and evaluate · Psychoeducation · General parenting skills · Specific parenting skills for children with CHD
Pediatric cardiologist	· Information on medical diagnoses, treatments, future issues (e.g., career, pregnancy), insurance, and healthy living (e.g., sports, diet)
Child workshop	
Health care professionals	**Content**
Psychologists	· Relaxation · Promoting autonomy · Strengthening self-esteem · Making friends · Problem solving skills · Positive thinking
Physiotherapists	· Playful, age-attuned sports exercises: warming-up, fitness, gross motor skills, balance, aiming and catching

Parent module

The parent module is based on the evidence-based CHIP-School protocol [2].

Workshop. The parent workshop focuses on problem prevention therapy, psychoeducation, general parenting skills, skills specific to parenting a child with CHD (given by two senior psychologists with expertise in the field; 4 hours), and medical issues (given by a pediatric cardiologist; 1 hour). The lunch break (1 hour) offers families more opportunity to interact and share (similar) experiences. During

the workshop, parents receive a manual which contains an overview of the topics that will be covered during the workshop and a home assignment on problem prevention therapy. Parents also receive handouts and a teacher information leaflet.

Follow-up booster session. Approximately four weeks after the workshop, parents receive an individual follow-up booster session with a psychologist who was present during the parent workshop and a psychologist who was present during the child workshop. Questions or worries that may have come up after the workshop regarding their child with CHD or their family members are discussed. Also, aspects of the workshop which have been (most) helpful for parents and will be helpful in the future are reviewed. Moreover, the session focuses on the problem prevention home assignment and on how to promote future use of problem prevention therapy.

Child module

To normalize participation in the workshop and to stimulate practice at home, each child is allowed to bring a 4- to 10-year-old sibling or friend. The psychological exercises (given by two junior psychologists; 4 hours) are based on the evidence-based cognitive behavioral therapy Fun FRIENDS protocol [26]. The exercises are provided in a playful manner and focus on regulating emotions, relaxation, promoting autonomy, strengthening self-esteem, making friends, problem solving skills, and positive thinking. The playful, age-attuned sports exercises (given by a physiotherapist and assistant physiotherapist; 1 hour) are based on a standardized training program. Previous research has shown that these exercises are effective in improving the quality of life in children with CHD [12].

Training and protocol adherence

CHIP-Family is performed in a standardized manner. Prior to the workshops, four senior and five junior psychologists receive a one-day CHIP-training by developmental psychologists Prof. McCusker and Dr. Doherty, developers of the original CHIP-protocol. To ensure consistency, the same senior and junior psychologist will be present at each workshop. In both the parent and child workshops, another psychologist will be present. Master's students in Psychology will assess treatment integrity during the parent and child workshop through a standardized form. Follow-up sessions are audiotaped and treatment integrity is assessed through a standardized form afterwards.

Outcome measures

An overview of all variables and questionnaires per assessment moment is given in Table 3. All questionnaires are (inter)nationally validated and Dutch normative data is available. Children and their families are enrolled into the study in groups of 6 to 10 families (3 to 5 families in the CHIP-group and 3 to 5 families in the CAU group). In both the CHIP-Family and the CAU condition, the first assessment will take place within 2 weeks before the CHIP-Family intervention (T1) and the follow-up post-assessment (T2) will take place 6 months after T1. Patients who are randomized into the CHIP-Family intervention group complete a social validity questionnaire assessing satisfaction with regards to the CHIP-program within 2 weeks after the intervention and at T2. All questionnaires are completed at home through a secure website.

Primary outcomes

Child behavioral/emotional problems. The problem section of the Child Behavior Checklist (CBCL) [28] 1,½-5 (100 items; for 4- and 5-year-olds) and CBCL/6-18 (120 items; for 6- and 7-year-olds) will be used to obtain standardized parent reports of emotional and behavioral problems in their child. Response categories range from 0 to 2, with higher scores indicating more emotional and/or behavioral problems. Adequate reliability and validity have been reported[29].

Parental mental health. The Symptom Checklist-90-Revised (SCL-90-R) [30] is a self-report scale (90 items; response categories: 1-5, higher score indicates more symptoms) which assesses 9 primary symptom dimensions: Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism. Adequate reliability and validity have been reported for the Dutch version [30].

Secondary outcomes

School days sick/absent. Through the Rotterdam Quality of Life interview [31] parents and teachers will be asked how many days the child was absent from school and what the reasons for absence were.

Disease-specific knowledge and illness perception. The Rotterdam Knowledge Questionnaire for Congenital Heart Disease [32] is used to assess parents' knowledge about CHD and parents' illness perception.

School functioning. The Dutch version of the Teacher's Report Form (C-TRF) 1½-5 (100 items)[33] or the TRF/6-18 (120 items) [34] will be completed by the teacher of the child. The TRF assesses problem behavior (at school). Response categories range from 0 to 2, with higher scores indicating more emotional and/or behavioral problems.

Executive functioning. The Dutch Behavior Rating Inventory of Executive Functioning (BRIEF)[35, 36] (63 items; 2-5 years) and BRIEF-Preschool version (BRIEF-P)[37] (63 items; 5-18 years) will be used to assess executive functioning skills in daily life. Response categories range from 0 to 2, with higher scores indicating more problems.

Enjoyment of leisure-time physical activity. The Groningen Enjoyment Questionnaire (GEQ; 10 items; response categories 1-3, higher score indicates more enjoyment) [38, 39] is adjusted for parents assesses enjoyment of physical activity. Children themselves answer two questions to assess how often they engage in physical activity and to assess enjoyment of physical activity.

Parental worry. The Penn State Worry Questionnaire (PSWQ; 16 items; response categories 1-5, higher score indicates higher level of worry)[40] assesses the excessiveness and uncontrollability of parental worry.

Parenting stress. The Nijmeegse Ouderlijke Stress Index verkort (NOSIK)[41, 42] (25 items; response categories 1-6, higher score indicates higher level of stress) measures stress due to parenting. Parents will also complete the Distress Thermometer (DT-P) [43] (40-42 items), which consists of a problem list and a thermometer on which parents are asked to rate their overall distress.

Quality of life of children and siblings. The Child Health Questionnaire Parent Form-50 (CHQ-PF50; 50 items)[44] is used to assess quality of life of the child with CHD and, if possible, of one sibling.

Parental quality of life. The Short-form (36) Health Survey (SF-36) [47] (36 items; score per domain 0-100, higher score indicates less disability) assesses eight health status domains: physical functioning, role limitations due to physical problems, bodily pain, general health, social functioning, role limitations due to emotional functioning, mental health, and vitality.

Family functioning. The general functioning subscale of the Family Assessment Device (FAD) [45] (12 items; response categories 1-4, higher total score indicates poorer functioning) assesses problem areas of family functioning.

Social validity. Through a questionnaire, parents will be asked about their satisfaction regarding CHIP-Family. Furthermore, data on attendance and completion of CHIP-Family will be recorded.

Predictors

Demographic variables. Demographic variables such as age, gender, and socio-economic status will be assessed through the Rotterdam Quality of Life interview [31].

Medical variables. Information about cardiac diagnosis, surgery, and intrusive procedures will be retrieved from medical records.

Life events. The 'life events' subscale of the Cognitive Emotion Regulation Questionnaire child version (CERQ-k) [47] is adjusted as such that parents can answer the questions about their child.

Table 3 Assessment instruments and moments of assessment.

		Assessment moment		
Instrument	**Variable**	**T1**	**Direct follow-up**	**T2**
Primary outcomes				
· Child Behavior Checklist (CBCL) [33]	Child behavioral/ emotional problems	M, F		M, F
· Symptom Checklist-90-Revised (SCL-90-R) [30]	Parental mental health	M, F		M, F
Secondary outcomes				
· Rotterdam Quality of Life interview [31]	School days sick/absent	M, F		M, F, T
· Rotterdam Knowledge Questionnaire [32]	Disease-specific knowledge and illness perception	M, F		M, F
· Teacher Report Form (TRF) [33]	School functioning			T

Table 3 Continued

		Assessment moment		
Instrument	**Variable**	**T1**	**Direct follow-up**	**T2**
· Behavior Rating Inventory of Executive Functioning (BRIEF) [35, 36] or BRIEF-Preschool Version (BRIEF-P) [37]	Executive functioning	M, F		M, F, T
· Adjusted Groningen Enjoyment Questionnaire [38]	Sports participation, enjoyment of physical activity	M, F		M, F, T
· 2 sports-related questions	Sports participation, enjoyment of physical activity	C		C
· Pennstate Worry Scale (PSWQ) [51]	Parental worry	M, F		M, F
· Nijmeegse Ouderlijke Stress Index verkort (NOSIK) [41]	Parental stress	M, F		M, F
· Stress thermometer (DT-P) [52]	Parental stress	M, F		M, F
· Child Health Questionnaire (CHQ-PF50) [53]	Quality of life of child and sibling	M, F		M, F
· Short-form (36) Health Survey (SF-36) [54]	Quality of life of parents	M, F		M, F
· Family Assessment Device, general functioning subscale (FAD) [55]	Family functioning	M, F		M, F
· Medical record	Medical consumption	R		R
· Social validity questionnaire	Satisfaction, attendance, and completion of CHIP-Family	-	M, F	M, F
Predictor variables				
· Rotterdam Quality of Life interview [31]	Demographic variables	M, F		-
· Medical record	Cardiac diagnosis	R		R
· Life event subscale of the Cognitive Emotion Regulation Questionnaire, child version (CERQ-k) [47]	Life events	M, F		M, F

M=Mother; F=Father; C=Child; T=Teacher; R=Medical records.
T1=baseline; Direct follow-up=within 2 weeks after CHIP-Family intervention (only for participants in intervention group); T2=follow-up, 6 months after T1.

Sample size calculation
To conduct a repeated measures ANOVA with two assessment moments, Cohen's d of 0.6, an alpha of .05 (two-tailed), and a power of .80, a sample size of 90 patients is needed, of which 45 patients in the intervention group.

Statistical analysis
To test the effectiveness of CHIP-Family on the primary outcome measures (for parents: mental health [SCL-90-R]; for children: behavioral/emotional problems [CBCL]) repeated measures ANOVAs will be conducted, for parental and child outcomes separately. Group (CHIP-Family versus CAU) will be the between-subjects variable and assessment (T1 versus T2) will be the within-subjects variable. Likewise, repeated measures ANOVAs will be conducted for the secondary outcome measures.

Additional regression analyses will be conducted to investigate in what way demographic factors, medical factors, and life events moderate the effect of CHIP-Family on the primary outcome measures.

DISCUSSION

Several cohort and longitudinal studies have shown that there is a compelling need for a family-based psychosocial intervention for children with CHD and their families [1-3, 18-21]. Since key milestones such as starting kindergarten and primary school present more challenges for children with CHD and their parents than for families with healthy children [20], an intervention tailored to their needs when starting school is needed. The previously examined CHIP-School intervention [2], the only evidence-based psychosocial intervention for this population to date, significantly improved maternal mental health, diminished perceived strain on the family, and resulted in less school absence of the child. However, CHIP-School targeted parents only, aiming for an indirect effect on child psychosocial wellbeing. CHIP-School resulted in a non-significant, though positive, increase in child psychosocial wellbeing.

To improve these outcomes, we will modify and extend CHIP by adding a tailored child module for children with CHD and their siblings, thereby creating the CHIP-Family intervention. The child module consists of evidence-based cognitive behavioral and sports exercises. We will conduct an RCT to examine the effect

of the innovated CHIP-Family intervention on parental mental health and psychosocial wellbeing of young children with CHD.

This study has several strengths. Firstly, if CHIP-Family proves to be effective, this would be the first evidence-based psychosocial intervention for young children with CHD and their families, thus meeting the previously described need for an intervention. Secondly, as recommended by the guidelines of the Association for European Pediatric Cardiology working group [22], CHIP-Family provides early intervention. CHIP-Family aims to reduce and prevent psychosocial problems. As mental health problems in childhood may persist into adulthood [22, 48], the prevention of psychosocial problems is important. Thirdly, CHIP-Family is a family-centered intervention. It is widely acknowledged that family functioning and parental factors play an important role in children's development [2, 14, 15]. As parents of children with CHD are at risk for psychosocial problems [19], a family-centered intervention may reduce their problems [49]. This, in turn, may enhance family functioning. Furthermore, siblings are involved in the workshop and receive attention from the hospital staff, which normalizes the position of the child with CHD.

In conclusion, this intervention aims to fulfill the need for an evidence-based family-centered psychosocial intervention for children with CHD and their families. If CHIP-Family proves to be effective in improving parental mental health and psychosocial wellbeing of children with CHD, it should be structurally implemented in standard care.

ACKNOWLEDGEMENTS

We gratefully acknowledge the Dutch Patient Association for Congenital Heart Disease and Stichting Kind & Ziekenhuis (the Dutch Association for Children in Hospital) for their advice on the study protocol.

FUNDING

This research project is funded by Fonds NutsOhra (101.083). The funding source had no role in the design of the study, and will not have any role in its execution, analysis, interpretation of the data, or decision to submit results.

AUTHORS' CONTRIBUTIONS

All authors critically reviewed the manuscript for intellectual content. All authors read and approved the final manuscript. Furthermore, MvdM drafted the initial manuscript and submitted the manuscript for publication. EU, WH, EvG, and KD were responsible for study concept, design, and funding. IvB was involved in funding and provided intellectual input for the CHIP-Family intervention. JvdE supervised statistical analyses. JD, LR, and TvdA provided intellectual input for the CHIP-Family intervention. AB provided intellectual feedback on the study design. CM and FC developed the original CHIP-protocol and were involved in drafting the grant application.

COMPETING INTERESTS

The authors confirm that they have no competing interests or affiliations to declare.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Medical Ethics Committee of the Erasmus Medical Center approved this trial (NL56872.078.16). This study was registered in the Dutch Trial Registry (NTR6063). This study will be conducted according to the Helsinki Declaration. Informed written consents will be obtained from the parents or guardians of the participating children. Netherlands Trial Registry: NTR6063.

REFERENCES

1. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012; 126(9): 1143-72.
2. McCusker CG, Doherty NN, Molloy B, Rooney N, Mulholland C, Sands A, et al. A randomized controlled trial of interventions to promote adjustment in children with congenital heart disease entering school and their families. J Pediatr Psychol. 2012; 37(10): 1089-103.
3. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, et al. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. Eur Heart J. 2003; 24(7): 673-83.
4. Spijkerboer AW, Utens EM, Bogers AJ, Helbing WA, Verhulst FC. A historical comparison of long-term behavioral and emotional outcomes in children and adolescents after invasive treatment for congenital heart disease. J Pediatr Surg. 2008; 43(3): 534-9.
5. Utens EM, Verhulst FC, Meijboom FJ, Duivenvoorden HJ, Erdman RA, Bos E, et al. Behavioural and emotional problems in children and adolescents with congenital heart disease. Psychol Med. 1993; 23(2): 415-24.
6. Karsdorp PA, Everaerd W, Kindt M, Mulder BJ. Psychological and cognitive functioning in children and adolescents with congenital heart disease: a meta-analysis. J Pediatr Psychol. 2007; 32(5): 527-41.
7. Menahem S, Poulakis Z, Prior M. Children subjected to cardiac surgery for congenital heart disease. Part 1 - emotional and psychological outcomes. Interact Cardiovasc Thorac Surg. 2008; 7(4): 600-4.
8. Bellinger DC, Newburger JW. Neuropsychological, psychosocial, and quality-of-life outcomes in children and adolescents with congenital heart disease. Progr Pediatr Cardiol. 2010; 29(2): 87-92.
9. Wernovsky G. Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. Cardiol Young. 2006; 16(1): 92-104.
10. Opic P, Roos-Hesselink JW, Cuypers JA, Witsenburg M, van den Bosch A, van Domburg RT, et al. Psychosocial functioning of adults with congenital heart disease: outcomes of a 30-43 year longitudinal follow-up. Clin Res Cardiol. 2015; 104(5): 388-400.
11. Zomer AC, Vaartjes I, Uiterwaal CS, van der Velde ET, Sieswerda GJ, Wajon EM, et al. Social burden and lifestyle in adults with congenital heart disease. Am J Cardiol. 2012; 109(11): 1657-63.
12. Dulfer K, Duppen N, Kuipers IM, Schokking M, van Domburg RT, Verhulst FC, et al. Aerobic exercise influences quality of life of children and youngsters with congenital heart disease: a randomized controlled trial. J Adolesc Health. 2014; 55(1): 65-72.

13. Dulfer K, Helbing WA, Duppen N, Utens EMWJ. Associations between exercise capacity, physical activity, and psychosocial functioning in children with congenital heart disease: a systematic review. Eur J Prev Cardiol. 2014; 21(10): 1200-15.

14. McCusker CG, Doherty NN, Molloy B, Rooney N, Mulholland C, Sands A, et al. A controlled trial of early interventions to promote maternal adjustment and development in infants born with severe congenital heart disease. Child Care Health Dev. 2010; 36(1): 110-7.

15. Jackson AC, Liang RPT, Frydenberg E, Higgins RO, Murphy BM. Parent education programmes for special health care needs children: A systematic review. J Clin Nurs. 2016; 25(11-12).

16. Landolt MA, Ystrom E, Stene-Larsen K, Holmstrom H, Vollrath ME. Exploring causal pathways of child behavior and maternal mental health in families with a child with congenital heart disease: A longitudinal study. Psychol Med. 2014; 44(16): 3421–33.

17. Casey FA, Stewart M, McCusker CG, Morrison ML, Molloy B, Doherty N, et al. Examination of the physical and psychosocial determinants of health behaviour in 4-5-year-old children with congenital cardiac disease. Cardiol Young. 2010; 20(5): 532-7.

18. Lawoko S, Soares JJ. Quality of life among parents of children with congenital heart disease, parents of children with other diseases and parents of healthy children. Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation. 2003; 12(6): 655-66.

19. Lawoko S, Soares JJ. Psychosocial morbidity among parents of children with congenital heart disease: a prospective longitudinal study. Heart Lung. 2006; 35(5): 301-14.

20. Tong EM, Kools S. Health care transitions for adolescents with congenital heart disease: patient and family perspectives. Nurs Clin North Am. 2004; 39(4): 727-40.

21. Lesch W, Specht K, Lux A, Frey M, Utens E, Bauer U. Disease-specific knowledge and information preferences of young patients with congenital heart disease. Cardiol Young. 2014: 1-10.

22. Utens E, Callus, E., Levert, E., De Groote, K., Casey, F. Multidisciplinary family-centred psychosocial care for patients with congenital heart disease. Guidelines from the AEPC Psychosocial Working group. Cardiol Young. in press.

23. Levert EM, Helbing WA, Dulfer K, van Domburg RT, Utens EM. Psychosocial needs of children undergoing an invasive procedure for a CHD and their parents. Cardiol Young. 2016: 1-12.

24. Spijkerboer AW, Utens EMWJ, Bogers AJJC, Verhulst FC, Helbing WA. Long-term intellectual functioning and school-related behavioural outcomes in children and adolescents after invasive treatment for congenital heart disease. Br J Dev Psychol. 2008; 26(4): 457-70.

25. Pahl KM, Barrett PM. Preventing Anxiety and Promoting Social and Emotional Strength in Preschool Children: A Universal Evaluation of the Fun FRIENDS Program. Adv Sch Ment Health Promot. 2010; 3(3): 14-25.

26. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. J Pharmacol Pharmacother. 2010; 1(2): 100-7.

27. D'Zurilla TJ, Nezu AM. Problem-Solving Therapy. In: Dobson KS, editor. Handbook of Cognitive-Behavioral Therapies 3rd edition New York: The Guilford Press; 2010.

28. Achenbach TM, Rescorla LA. Manual for the ASEBA school-age forms & profiles. . Burlington, Vermont: University of Vermont, Research Center for Children, Youth, & Families,; 2001.

29. Achenbach TM, Becker A, Dopfner M, Heiervang E, Roessner V, Steinhausen HC, et al. Multicultural assessment of child and adolescent psychopathology with ASEBA and SDQ instruments: research findings, applications, and future directions. J Child Psychol Psyc. 2008; 49(3): 251-75.

30. Arrindell WA, Ettema JHM. SCL-90. Symptom Checklist. Handleiding bij een multidimensionele psychopathologie-indicator. Lisse: Swets Test Publishers; 2003.

31. Utens E, Dulfer K. Rotterdams Kwaliteit van Leven Interview. 2010.

32. Utens EMWJ, Dulfer K. Rotterdam Knowledge Questionnaire. 2010.

33. Achenbach TM, Rescorla LA. Manual for ASEBA Preschool Forms & Profiles. Burlington: University of Vermont, Research Center for Children, Youth and Families; 2000.

34. Verhulst FC, Ende Jvd. Handleiding ASEBA Vragenlijsten voor leeftijden 6 tot en met 18 jaar. Rotterdam, The Netherlands: ASEBA; 2013.

35. Smidts DP, Huizinga M. BRIEF Executieve Functies Gedragsvragenlijst: Handleiding. Amsterdam: Hogrefe Uitgevers; 2009.

36. Gioia GA, Isquith PK, Guy SC, Kenworthy L. Behavior rating inventory of executive function: BRIEF. Odessa, FL: Psychological Assessment Resources; 2000.

37. Van der Heijden KB, J. S, De Sonneville LMJ, Swaab HJT. BRIEF-P Vragenlijst executieve functies voor 2- tot 5-jarigen. Amsterdam: Hogrefe uitgevers; 2013.

38. Stevens M, Moget P, De Greee MH, Lemmink KA, Rispens P. The Groningen Enjoyment Questionnaire: a measure of enjoyment in leisure-time physical activity. Percept Mot Skills. 2000; 90(2): 601-4.

39. Dulfer K, Duppen N, Blom NA, van Dijk AP, Helbing WA, Verhulst FC, et al. Effect of exercise training on sports enjoyment and leisure-time spending in adolescents with complex congenital heart disease: the moderating effect of health behavior and disease knowledge. Congenit Heart Dis. 2014; 9(5): 415-23.

40. van der Heiden C, Muris P, Bos AE, van der Molen HT. Factor structure of the Dutch version of the Penn State Worry Questionnaire. J Behav Ther Exp Psychiatry. 2010; 41(3): 304-9.

41. Brock AJLL, Vermulst AA, Gerris JRM, Abidin RR. NOSI, Nijmeegse Ouderlijke Stress Index, handleiding. 1992.

42. Abidin RR. Parenting Stress Index. third ed. Lutz, Florida: Psychological Assessments Resources, Inc; 1983.

43. Haverman L, van Oers HA, Limperg PF, Houtzager BA, Huisman J, Darlington AS, et al. Development and validation of the distress thermometer for parents of a chronically ill child. J Pediatr. 2013; 163(4): 1140-6.

44. Landgraf JM, Abetz L, Ware JE. The CHQ user's manual. Second printing. Boston, MA: HealthAct. 1999.

45. Epstein NB, Baldwin LM, Bishop DS. The McMaster Family Assessment Device. J Marital Fam Ther. 1983; 9(2): 171-80.

46. Garnefski N, Rieffe C, Jellesma F, Terwogt MM, Kraaij V. Cognitive emotion regulation strategies and emotional problems in 9 - 11-year-old children: the development of an instrument. Eur Child Adolesc Psychiatry. 2007; 16(1): 1-9.

47. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the Penn State Worry Questionnaire. Behaviour research and therapy. 1990; 28(6): 487-95.

48. Tuinman MA, Gazendam-Donofrio SM, Hoekstra-Weebers JE. Screening and referral for psychosocial distress in oncologic practice: use of the Distress Thermometer. Cancer. 2008; 113(4): 870-8.

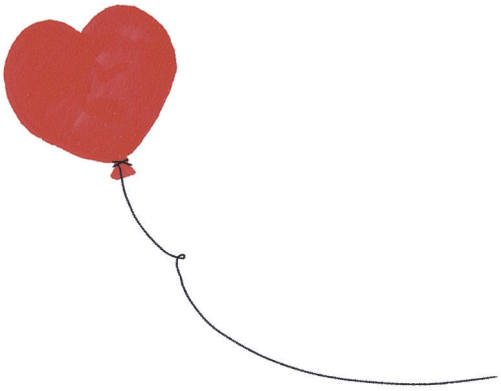
49. Hullmann SE, Ryan JL, Ramsey RR, Chaney JM, Mullins LL. Measures of general pediatric quality of life: Child Health Questionnaire (CHQ), DISABKIDS Chronic Generic Measure (DCGM), KINDL-R, Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales, and Quality of My Life Questionnaire (QoML). Arthritis Care. 2011; 63(11): 420-30.

50. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol. 1998; 51(11): 1055-68.

51. Epstein L. Family and community medicine: complementary components of primary health care. Isr J Med Sci. 1983; 19(8): 719-22.

52. Hofstra MB, van der Ende J, Verhulst FC. Child and adolescent problems predict DSM-IV disorders in adulthood: a 14-year follow-up of a Dutch epidemiological sample. J Am Acad Child Adolesc Psychiatry. 2002; 41(2): 182-9.

53. Law EF, Fisher E, Fales J, Noel M, Eccleston C. Systematic review and meta-analysis of parent and family-based interventions for children and adolescents with chronic medical conditions. J Pediatr Psychol. 2014; 39(8): 866-86.



4

CHAPTER 4

CHIP-Family intervention to improve the psychosocial well-being of young children with congenital heart disease and their families: results of a randomized controlled trial

Malindi van der Mheen, Maya G. Meentken, Ingrid M. van Beynum, Jan van der Ende, Eugène van Galen, Anne Zirar, Elisabeth W.C. Aendekerk, Tabitha P.L. van den Adel, Ad J.J.C. Bogers, Christopher G. McCusker, Manon H.J. Hillegers, Willem A. Helbing, Elisabeth M.W.J. Utens

Cardiology in the Young, 2019, 29 (9), 1172-1182

ABSTRACT

Objective. Children with congenital heart disease and their families are at risk of psychosocial problems. Emotional and behavioral problems, impaired school functioning, and reduced exercise capacity often occur. To prevent and decrease these problems, we modified and extended the previously established Congenital Heart Disease Intervention Program (CHIP) - School, thereby creating CHIP-Family. CHIP-Family is the first psychosocial intervention with a module for children with congenital heart disease. Through a randomized controlled trial, we examined the effectiveness of CHIP-Family.

Methods. Ninety-three children with congenital heart disease (age M=5.34 years, SD=1.27) were randomized to CHIP-Family (N=49) or care as usual (no psychosocial care; N=44). CHIP-Family consisted of a one-day group workshop for parents, children, and siblings and an individual follow-up session for parents. CHIP-Family was delivered by psychologists, pediatric cardiologists, and physiotherapists. At baseline and 6-month follow-up, mothers, fathers, teachers, and the child itself completed questionnaires to assess psychosocial problems, school functioning, and sports enjoyment. Moreover, at 6-month follow-up, parents completed program satisfaction assessments.

Results. Although small improvements in child outcomes were observed in the CHIP-Family group, no statistically significant differences were found between outcomes of the CHIP-Family and care as usual group. Mean parent satisfaction ratings ranged from 7.4 to 8.1 (range 0–10).

Conclusions. CHIP-Family yielded high program acceptability ratings. However, compared to care as usual, CHIP-Family did not find the same extent of statistically significant outcomes as CHIP-School. Replication of promising psychological interventions, and examination of when different outcomes are found, is recommended for refining interventions in the future.

INTRODUCTION

Children with congenital heart disease (CHD) are at increased risk of a range of psychosocial problems. Therefore, the aim of the current study was to determine the effectiveness of an innovative psychosocial intervention, the Congenital Heart Disease Intervention Program (CHIP) – Family, in improving the psychosocial well-being of children with CHD and their families. The arguments for reducing psychosocial problems in these families are discussed below.

In children with CHD, emotional and behavioral problems may already emerge in infancy [1, 2]. Compared with healthy children, preschool and school-aged children with CHD have increased levels of internalizing and externalizing problems [3-8] and reduced levels of school performance [5, 7, 9]. Moreover, compared with healthy children, children with CHD more often require remedial teaching or special education [10-14] and face increased rates of grade repetition [4, 12, 15]. Impaired social functioning and social cognition have also been reported [5, 9, 16]. Children with CHD participate in fewer social activities [14] and are more often perceived to be withdrawn, not accepted by peers, and too dependent on others [9]. In adolescence and adulthood, CHD patients remain at increased risk of psychosocial difficulties [17-22].

As to physical activity levels of children with CHD, conflicting results have been reported. Several studies, including two systematic reviews, have reported reduced levels of physical activity in children with severe CHD [23-26]. However, others have found that physical activity levels of children with different CHD diagnoses do not differ from those of children from the general population [27].

It is increasingly recognized that parental mental well-being mediates psychosocial outcomes in children with CHD [4, 9] and that family factors are more important predictors of psychosocial outcomes of children with CHD compared to medical factors [28, 29]. Unfortunately, parents of children with CHD themselves are at increased risk of mental health problems, such as posttraumatic stress disorder, depression, and anxiety [30-32].

To prevent and decrease these difficulties in children with CHD and their families, a multidisciplinary, psychosocial intervention is needed. Research has demonstrated that families of children with CHD express a need for psychosocial care themselves [33, 34]. Until now, the only evidence-based psychosocial intervention in this field

was the CHIP-School program [35, 36]. CHIP-School consisted of a multidisciplinary 1-day group workshop and individual follow-up session for parents of children with CHD who were entering school. The theoretical rationale of CHIP-School was derived from Thompson's transactional stress and coping model [37]. This model states that the effect of an illness on a child's well-being is mediated by familial coping and appraisal. The developers aimed to strengthen parental mental health and parenting skills, thereby indirectly increasing emotional resilience of children with CHD. CHIP-School yielded positive results with regard to maternal mental health, perceived strain on the family, and school absence of the child. With regard to child emotional and behavioral problems, no significant improvements were found. However, CHIP-School did not contain a specific child module. We reasoned that directly targeting both parents and children would improve the results previously obtained through CHIP-School.

Therefore, we have modified CHIP-School and added a specific child module specifically focused on improving emotional well-being, sports enjoyment, and school functioning. As mothers, fathers, and siblings are also part of this innovated and extended intervention, the intervention is titled "CHIP-Family". We hypothesized that participating in the CHIP-Family intervention would improve the psychosocial well-being of children with CHD and their parents, family functioning, and parents' disease-specific knowledge.

METHODS

This single-blinded parallel randomized controlled trial was approved by the Medical Ethics Committee of the Erasmus Medical Center and adhered to the ethical guidelines of the Declaration of Helsinki. Before participation, written informed consent was obtained from all patients' parents or legal guardians. A detailed description of the study protocol has been published previously [38].

Participants

Children and their families were recruited during a one-year inclusion period (30 September 2016 to 12 September 2017) via the Erasmus Medical Center – Sophia Children's Hospital, a tertiary referral center for pediatric cardiology and cardiac surgery in the Netherlands, and nationally via the Dutch Patient Association for Congenital Heart Disease. Families of children who (1) underwent at least one invasive medical procedure for CHD (i.e., cardiac catheterization and/or open heart surgery) and (2) were attending kindergarten or first or second year of primary

school at the time of first assessment, were eligible for participation. Children with known intellectual impairment (intelligence quotient ≤ 70) were excluded, as a sufficient level of intelligence was required to participate in the child intervention program. Moreover, prematurely born children (i.e., gestational age at birth < 37 weeks) with no other CHD than a patent ductus arteriosus were excluded, as families of prematurely born children experience different psychosocial problems [39]. Lastly, sufficient mastery of the Dutch language was required.

Procedure

As to patients of the Erasmus Medical Center, eligibility was assessed by screening patient records of 2- to 8-year-old children who had undergone an invasive cardiac procedure or who had received cardiac follow-up. Subsequently, parents of children who seemed to be eligible received an information letter explaining the purpose and content of the study. As to members of the Dutch Patient Association for Congenital Heart Disease, for privacy reasons, no medical information was available. Therefore, information letters explaining the purpose and content of the study were sent to parents of all 2- to 8-year-old children.

If parents indicated to be interested in participation or did not respond within 2 weeks, eligibility was verified via a phone call. Before giving written informed consent, all families received a verbal explanation of the study and were invited to ask questions. Consequently, an independent researcher randomly assigned participants to the CHIP-Family intervention or care as usual control group, which only received medical care (allocation ratio 1:1). The researcher who collected all assessments and performed all analyses was blinded for randomization outcome. Randomization was stratified by school year (kindergarten versus primary school) and CHD severity. CHD severity was divided into limited to no residual heart defects versus mild to severe residual heart defects after cardiac intervention (see Table 1). This classification was made based on treatment-related aspects and intensity of cardiac follow-up [40]. Randomization block size was fixed at four per stratification category. Due to logistical reasons in the starting phase of the project, the first four families who consented to participate were allocated to the CHIP-Family group without randomization. We limited the period between baseline assessment and the intervention to 2 weeks. Moreover, parents had to be notified earlier that they had to make practical arrangements to be able to participate in the CHIP-Family workshop for an entire day. For these two important logistic reasons, parents of patients were informed of randomization outcome prior to the baseline

assessment. The follow-up assessment took place 6 months after baseline. The participation flow-chart is shown in Figure 1.

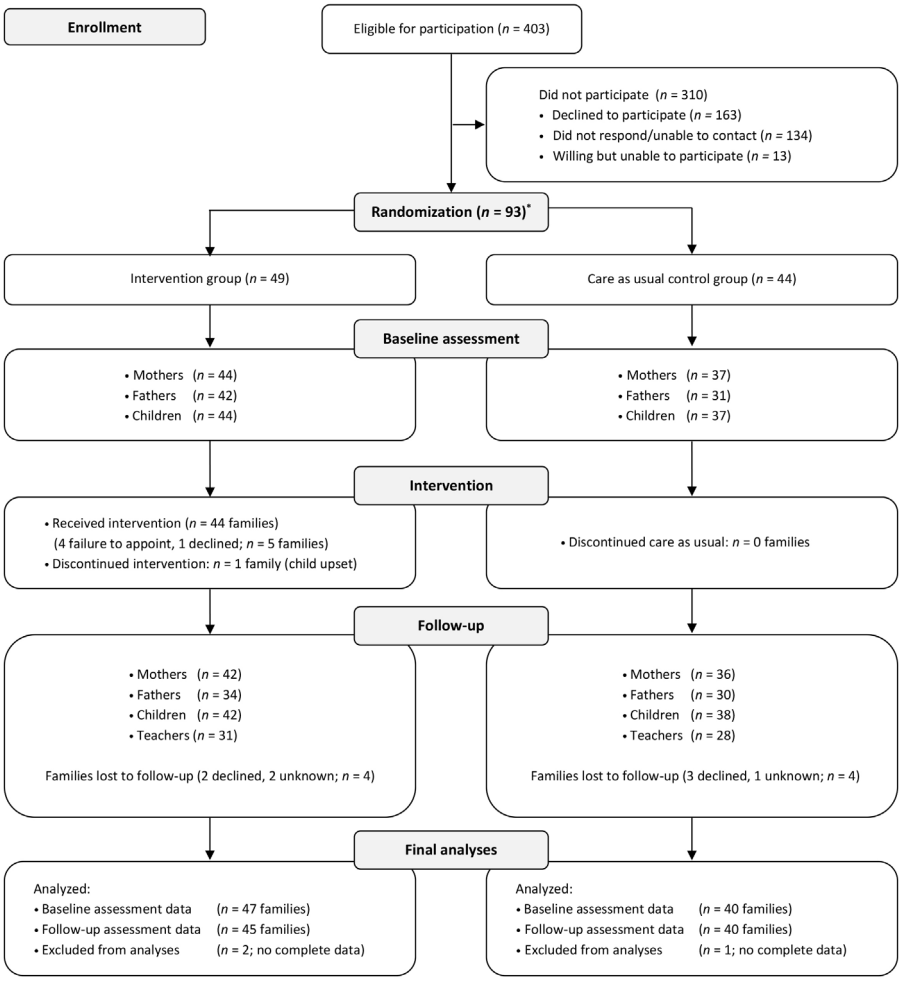
Table 1 Stratification factor "CHD severity".

Residual heart defects after cardiac intervention	
Limited to none	**Mild to severe**
Atrial Septal Defect (ASD) Patent Ductus Arteriosus Pulmonary valve stenosis Total Anomalous Pulmonary Venous Connection Ventricular Septal Defect (VSD)	Anomalous Left Coronary Artery from the Pulmonary Artery (ALCAPA) Atrioventricular Septal Defect (AVSD) Coarctation of the Aorta Complex Biventricular (e.g. Truncus Arteriosus, aortic arch defects with VSD) Univentricular heart defects – Fontan circulation Ebstein's Anomaly (Sub)valvular Aortic Stenosis Tetralogy of Fallot (TOF); including with Main Aorta to Pulmonary Connecting Artery (MAPCA) Transposition of the Great Arteries

Intervention

The CHIP-Family intervention is an adaptation and extension of the CHIP-School intervention [36]. CHIP-Family consisted of a 6-hour group workshop (three to five families per workshop) for parents and children and an individual 1-hour follow-up session per parent couple. The developers of the original CHIP-protocol conducted a 1-day training for four senior licensed clinical and health psychologists and five junior psychologists to deliver the parent module of the CHIP-Family intervention. A senior psychologist trained the junior psychologists to provide the child module. During the parent workshops and child workshops, protocol adherence was assessed through a standardized form by psychology master's students (one student per workshop). For privacy reasons and due to the group format of the CHIP-Family workshops, it was not possible to videotape or audiotape the workshops. With the consent of parents, protocol adherence of the individual follow-up sessions was assessed through audiotapes by psychology master's students.

Figure 1 Participation flowchart.



* 89 children and their families were randomly allocated to either the intervention group or care as usual control group. The first 4 children and their families were directly allocated to the CHIP-Family intervention group.

The 1-day parent workshop consisted of problem prevention therapy, psychoeducation, general parenting skills, skills specific to parenting a child with CHD (provided by two senior clinical psychologists for 4 hours), and medical issues (provided by a pediatric cardiologist supported by a senior clinical psychologist for 1 hour). The 1-hour lunch break gave families more opportunity to share their experiences.

As background information, parents received all slides that were presented in the workshop, the CHIP manual [41] containing all topics covered during the workshop, several information leaflets, and a home assignment on problem prevention therapy. Approximately 4 weeks after the workshop, each parent couple received an individual follow-up session provided by a senior psychologist who was present at the parent workshop and a psychologist who was present at the child workshop. The follow-up session focused on questions or worries of individual families, future coping strategies, and the problem prevention home assignment.

Whereas the CHIP-School intervention consisted of a parent module, the CHIP-Family module also comprised a specific child module. The child module consisted of a workshop that was held concurrently with the parent workshop. The child workshop consisted of cognitive behavioral exercises based on the evidence-based Fun FRIENDS protocol [42, 43] and focused on strengthening self-esteem, regulating emotions, relaxation, problem solving skills, and positive thinking (provided by two junior psychologists who were supervised by two senior clinical psychologists for 4 hours). The children also did sport exercises based on a standardized exercise program [44] specifically developed for children with CHD and their siblings (provided by a physiotherapist and assistant for 1 hour). Each child was allowed to bring a 4- to 10-year-old sibling or friend, to normalize participation and to stimulate practice at home.

Thus, though predicated on a similar conceptual model, CHIP-Family differed from CHIP-School by having parallel modules/workshops for the whole family (children, siblings, and parents). In addition, CHIP-School included a bicycle exercise stress test. This was essentially a behavioral experiment to highlight to parents (in vivo and in the presence of a cardiologist) that vigorous exercise was safe with non-concerning electrocardiogram rhythms evident throughout. Unfortunately, it was not possible to include this in the current CHIP-Family intervention for logistic reasons.

Instruments

All questionnaires were completed by both parents at baseline and 6-month follow-up, unless otherwise specified. Teachers completed only the 6-month follow-up questionnaires, because some teachers did not know the child sufficiently at baseline to fill out the questionnaires. If a child had multiple teachers, questionnaires were completed by the teacher who knew the child the best or spent the most time with the child. Children completed two sports-related questions

at baseline and 6-month follow-up. Validated Dutch versions of internationally well-known questionnaires with adequate psychometric properties were used. All questionnaires were completed through a secure online system. Demographic variables were assessed through the Rotterdam Quality of Life interview [45].

Child outcomes

Child emotional and behavioral problems were the primary child outcome and were assessed through the Child Behavior Checklist (CBCL) [46] 1,½-5 (100 items; for 4- and 5-year-olds) or CBCL/6-18 (120 items; for 6- to 8-year-olds).

Problem behavior at school was assessed through the Teacher's Report Form (C-TRF [47]) 1½-5 (100 items; for 4- and 5-year-olds) or the TRF/6-18 [47] (120 items; for 6- to 8-year-olds) which was completed by teachers.

Executive functioning was assessed through the Behavior Rating Inventory of Executive Functioning (BRIEF [48]; 63 items; for 6- to 8-year-olds) or BRIEF-Preschool version (BRIEF-P [49]; 63 items; for 4- and 5-year-olds) which was completed by parents and teachers.

Children's health related quality of life was assessed through the Child Health Questionnaire – Parent Form-50 (CHQ-PF50 [50]; 50 items).

School absence was assessed through the Rotterdam Quality of Life interview [45].

Children's enjoyment of physical activity was assessed through an adjusted version of the Groningen Enjoyment Questionnaire (GEQ [51, 52]; 10 items) which was completed by parents and teachers. The sentencing of the GEQ items was adjusted to enable parents and teachers to fill out the questionnaire (e.g., "This child likes being physically active" instead of "I like being physically active"). In addition to the GEQ, children themselves were asked to answer two questions indicating their enjoyment of physical activity and how often per week they engage in physical activity.

Parental and family outcomes

Parental mental health was the primary parental outcome and was assessed through the Symptom Checklist-90-Revised (SCL-90-R [53]; 90 items), which measures symptom severity of mental health problems.

Excessiveness and uncontrollability of parental worry were assessed through the Penn State Worry Questionnaire (PSWQ [54, 55]; 16 items).

Parenting stress was assessed through the short version of the Nijmeegse Ouderlijke Stress Index (NOSIK [56]; 25 items) and the Distress Thermometer (DT-P [57]; 42 items).

Parents' health related quality of life was assessed through the Short-form (36) Health Survey (SF-36 [58]; 36 items).

Family functioning was assessed through the general functioning subscale of the Family Assessment Device (FAD [59]; 12 items).

Parents' knowledge about CHD (10 items) was assessed through the Rotterdam Knowledge Questionnaire for Congenital Heart Disease [52, 60].

Program satisfaction was assessed through a social validity questionnaire which parents completed 2 weeks after CHIP-Family and at 6-month follow-up.

Statistical analyses

Differences in baseline participant characteristics between the CHIP-Family and the care as usual groups were examined using t-tests, chi-square tests, and Fisher's exact tests, where appropriate.

To determine the effectiveness of the CHIP-Family intervention, we compared the differences in change in parent- and child-reported outcomes over time between the CHIP-Family and care as usual group using generalized estimating equations (GEE) [61]. A GEE analysis accounts for the dependency between repeated observations and accommodates missing values [62]. The analyses were performed on an intention-to-treat basis. Patients were included in an analysis if an outcome was available at one or both assessment moments. For each outcome, we conducted separate GEE analyses. The interaction between time and group (i.e., CHIP-Family versus care as usual) was examined as the test of effectiveness of CHIP-family. We selected a normal distribution and an identity link function for the majority of outcomes. The SCL-90-R total score, DT-P total score, SF-36 physical component score, pleasure in sports reported by children, and sports participation per week were not normally distributed. Therefore, for these outcomes a gamma distribution with log link function was used.

Teacher-reported outcomes were only assessed at follow-up. We used t-tests to compare the difference in teacher-reported continuous outcomes between the CHIP-Family and care as usual group. Because the majority of children had not been absent from school the past month, school absence was dichotomized into 0 days absent and ≥ 1 day absent and presented as percentage. To compare the difference in school absence between the CHIP-Family and care as usual group, chi-square tests were applied.

For the primary outcome variables (CBCL and SCL-90-R), the significance level was set at $\alpha = .05$. To adjust for multiple testing within the secondary outcome variables of the child domain and the parental and family domain, we used a Bonferroni correction. In both domains, 17 tests were conducted. Therefore, results with $p < .003$ were considered statistically significant. All statistical analyses were performed using SPSS version 24 [63]. Sample size calculations can be found in a previous publication of the study design [38].

RESULTS

Participant characteristics

In total, 93 children were randomized into either the CHIP-Family (n = 49) or the care as usual group (n = 44). Non-participants' cardiac diagnosis and gender were only available for patients of the Erasmus MC – Sophia Children's Hospital (86.6% of eligible patients) and not for patients contacted via the Dutch Patient Association for Congenital Heart Disease (13.4% of eligible patients). Participants and non-participants from the Erasmus MC – Sophia Children's Hospital did not differ as to CHD severity ($p = .06$) and gender ($p = .12$). Other demographic data were not available.

Parents of three children did not complete any questionnaires after randomization. Therefore, the final sample consisted of 90 children (n = 47 CHIP-Family, n = 43 care as usual). The CHIP-Family and care as usual group did not differ from each other in terms of age, gender, CHD type, school year, recruitment center, comorbid physical illness, family composition, or social economic status (see Table 2), which indicates that randomization was successful. Four children were referred for further psychological care after participating in the CHIP-Family intervention (n = 44) and received this care after completion of the follow-up assessment. Problems such as anxiety and emotion regulation issues were noted in these children during the group workshop and/or individual follow-up session.

Table 2 Baseline participant characteristics.

Characteristic	Intervention group (N = 47)	Control group (N = 43)	*p*-value
Child age, N	47	43	.426[a]
Mean years at baseline ± SD	5.43 ± 1.30	5.21 ± 1.26	
Child gender, N	47	43	.527[b]
Male, N (%)	25 (53.2%)	20 (46.5%)	
Residual heart defects after cardiac intervention, N	47	43	.844[b]
Limited to none[d], N (%)	14 (29.8%)	12 (27.9%)	
Mild to severe[d], N (%)	33 (70.2%)	31 (72.1%)	
Parent-reported comorbid physical illness, N	42	38	.867[b]
Any, N (%)	14 (29.8%)	12 (31.6%)	
School year at baseline, N	47	43	.791[c]
1 (kindergarten), N (%)	19 (40.4%)	20 (46.5%)	
2 (kindergarten), N (%)	10 (21.3%)	8 (18.6%)	
3 (primary school), N (%)	12 (25.5%)	12 (27.9%)	
4 (primary school), N (%)	6 (12.8%)	3 (7.0%)	
Child ethnicity, N	42	38	.728[c]
Dutch, N (%)	41 (97.6%)	37 (97.4%)	
Other, N (%)	1 (2.4%)	1 (2.6%)	
Family composition, N	42	38	.606[c]
Single parent, N (%)	2 (4.8%)	2 (5.3%)	
Both biological parents at home, N (%)	37 (88.1%)	36 (94.7%)	
Biological parent and partner, N (%)	3 (7.1%)	0 (0%)	
Mothers' highest completed education level[e], N	42	36	.394[c]
Low, N (%)	0 (0%)	2 (5.6%)	
Intermediate, N (%)	17 (40.5%)	15 (41.7%)	
High, N (%)	25 (59.5%)	19 (52.8%)	
Fathers' highest completed education level[e], N	36	29	.120[c]
Low, N (%)	1 (2.8%)	1 (3.4%)	
Intermediate, N (%)	12 (33.3%)	16 (55.2%)	
High, N (%)	23 (63.9%)	12 (41.4%)	

Table 2 Continued

Characteristic	Intervention group (N = 47)	Control group (N = 43)	*p*-value
Recruitment center, N	47	43	.484[b]
Academic children's hospital	33 (70.2%)	33 (76.7%)	
Patient association	14 (29.8%)	10 (23.3%)	

[a] T-test.

[b] Chi-square test.

[c] Fisher's exact test.

[d] Limited to none: Atrial Septal Defect (ASD), Patent Ductus Arteriosus, Pulmonary valve stenosis, Total Anomalous Pulmonary Venous Connection, Ventricular Septal Defect (VSD). Mild, moderate, severe: Anomalous Left Coronary Artery from the Pulmonary Artery (ALCAPA), Atrioventricular Septal Defect (AVSD), Coarctation of the Aorta, Complex Biventricular (e.g. Truncus Arteriosus, aortic arch defects with VSD), Univentricular heart defects – Fontan circulation, Ebstein's Anomaly, (Sub)valvular Aortic Stenosis, Tetralogy of Fallot (TOF); including with Main Aorta to Pulmonary Connecting Artery (MAPCA), Transposition of the Great Arteries.

[e] Low: primary education, lower vocational education, lower or middle general secondary education; Intermediate: middle vocational education, higher secondary education, pre-university education; High: higher vocational education, university.

Protocol adherence

Workshops. Five families randomized into the CHIP-Family group did not participate in the CHIP-Family intervention. Of these five families, one family declined to participate in CHIP-Family and four families were unable to attend the intervention due to practical reasons. In total, 44 families participated in the CHIP-Family workshops. One family discontinued the intervention after approximately 1 hour, because the child was upset.

Of 34 (77.3%) families, both parents participated in the workshop. Of the remaining 10 (22.7%) families, only the mother participated in the workshop. Twenty-eight (63.7%) children participated in the workshop with a sibling, 6 (13.6%) children participated with a friend, and 10 (22.7%) children participated without a sibling or friend. In nine parent workshops and seven child workshops, all the protocol topics were discussed. In the remaining two parent workshops and four child workshops, 96% of the protocol topics was discussed. This indicates excellent protocol adherence.

Follow-up sessions. Of all families, at least one parent attended the follow-up session. Four psychology master's students rated protocol adherence of a randomly selected 50% of the follow-up sessions. On average, 87% of the protocol topics was discussed in the randomly selected follow-up sessions.

Outcomes

Child, parental, and family outcomes are summarized in Tables 3 and 4. No statistically significant differences between the CHIP-Family and care as usual group were found in both the child outcomes (reported by children, mothers, fathers, and teachers) and the parental and family outcomes (reported by mothers and fathers).

Despite successful randomization, the baseline difference in CBCL total scores reported by mothers was statistically significant ($p = .001$), such that mothers in the CHIP-Family group reported more child emotional and behavioral problems at baseline than mothers in the care as usual group. No other baseline differences in outcomes were found. For both the CHIP-Family and the care as usual group, CBCL total scores reported by both mothers and fathers significantly decreased from baseline to follow-up ($p = .001$ and $p < .001$).

Program acceptability

Thirty-one (70.5%) mothers and 26 (76.5%) fathers who participated in CHIP-Family rated program acceptability at 6-month follow-up. On a scale of 0-10, mean overall usefulness rating was 7.5 (SD = 1.6) and 7.8 (SD = 1.5), respectively, for the parent and child workshop. Mean satisfaction rating was 7.7 (SD = 1.2) and 8.1 (SD = 1.3) for the parent and child workshop, respectively. Mean rating of the usefulness of the individual follow-up session was 7.4 (SD = 1.5). Mean rating of the likeliness that parents would recommend CHIP-Family to other families of children with CHD was 7.7 (SD = 1.5). Parents were asked to rate which components of CHIP-Family they found most useful (see Figure 2). Most parents perceived the psychosocial and medical explanation of the pediatric cardiologist (72.7%), meeting other families of children with CHD (61.8%), the child workshop (50.9%), and receiving skills tailored to parenting children with CHD (43.6%) as most useful elements of the intervention. At follow-up, a substantial percentage of parents (47.7%) reported using the techniques learnt in CHIP-Family sometimes (monthly).

Parents of children with less severe CHD (i.e., limited to no residual heart defects after cardiac intervention; see Table 1) rated usefulness of the child workshop more

favorably (M = 8.4, SD = 1.6) compared to parents of children with more severe CHD (i.e., mild to severe residual heart defects after cardiac intervention; see Table 1; M = 7.4, SD = 1.4), t(53) = 2.23, p = .03. Parents of children with less severe CHD also rated satisfaction with the child workshop more favorably (M = 8.6, SD = 1.3) compared to parents of children with more severe CHD (M = 7.8, SD = 1.2), t(53) = 2.47, p = .02.

DISCUSSION

The aim of the current randomized controlled trial was to examine the effect of the multidisciplinary, psychosocial CHIP-Family intervention on psychosocial well-being of young children with CHD and their families. Parents evaluated usefulness of and satisfaction with CHIP-Family positively. Moreover, through CHIP-Family, the involved mental health care professionals were able to identify four children who had psychosocial issues which required additional psychological care. These psychosocial issues might otherwise have remained unnoticed and untreated. However, our findings indicate that, compared with care as usual, participation in CHIP-Family did not significantly improve the psychosocial well-being of children with CHD and their families at 6-month follow-up. This is in contrast with the results of the previously examined CHIP-School intervention, which yielded more positive results at 10-month follow-up [36].

The culture of replicability research in psychological interventions in general is poor and publication bias often amplifies the problem [64]. However, replication studies not only are important to confirm or question the impact of an intervention, but rather to yield important information to further refine interventions and evaluation protocols. Thus, Stehl and colleagues [65] found that a similar family focused intervention for parents of children with cancer, whilst successful later in the illness trajectory, yielded less impressive outcomes when delivered earlier in the illness cycle – despite the promising theoretical reasons why it might be even more effective. Law and colleagues' [66] meta-analysis highlighted generally small to moderate effect sizes, and mostly on parental functioning in family-focused interventions ultimately aimed at improving outcomes for the child. Again, important lessons in intervention focus and measurements used were discussed.

Table 3 Child outcomes.

	Intervention group (N = 47)		Control group (N = 43)		*P*-value	Effect size
Outcome measure	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**		
Behavioral/emotional problems[a] - CBCL T-score total problem score						
Reported by mothers (N=84)	54.80 ± 9.50	52.25 ± 12.70	45.94 ± 10.36	45.50 ± 10.17	0.084[c]	0.59[f]
Reported by fathers (N=75)	49.72 ± 11.61	46.71 ± 11.86	45.76 ± 11.01	43.67 ± 9.87	0.293[c]	0.28[f]
School functioning[a] - (C-)TRF T-score total problem score						
Reported by teachers (N=59)	-	54.55 ± 9.20	-	53.54 ± 10.05	0.688[d]	0.10[f]
Executive functioning[a] - BRIEF(-P) T-score total score						
Reported by mothers (N=81)	48.20 ± 12.09	48.38 ± 11.95	47.00 ± 11.21	47.43 ± 13.08	0.964[c]	0.08[f]
Reported by fathers (N=72)	46.82 ± 13.43	44.06 ± 13.28	46.50 ± 12.30	46.25 ± 12.57	0.604[c]	0.17[f]
Reported by teachers (N=57)	-	47.00 ± 12.04	-	47.37 ± 10.43	0.902[d]	0.03[f]
Health-related quality of life[b] - CHQ-PF50 physical summary measure						
Reported by mothers (N=81)	47.70 ± 11.70	48.81 ± 9.75	49.09 ± 6.69	49.09 ± 7.93	0.976[c]	0.03[f]
Reported by fathers (N=70)	49.61 ± 13.04	51.12 ± 7.84	51.38 ± 8.21	50.53 ± 7.22	0.345[c]	0.08[f]
Health-related quality of life[b] - CHQ-PF50 psychosocial summary measure						
Reported by mothers (N=81)	52.16 ± 7.33	50.48 ± 10.60	53.82 ± 6.95	53.40 ± 6.95	0.491[c]	0.33[f]
Reported by fathers (N=70)	52.63 ± 8.25	53.46 ± 8.57	55.48 ± 5.57	55.10 ± 7.50	0.636[c]	0.20[f]

Table 3 Continued

Outcome measure	Intervention group (N = 47)		Control group (N = 43)		*P*-value	Effect size
	Baseline	Follow-up	Baseline	Follow-up		
≥1 days absent from school, past month						
Reported by mothers, n (%) (N=73)	-	15 (39.5%)	-	15 (42.9%)	0.769[e]	0.03[g]
Reported by fathers, n (%) (N=61)	-	13 (40.6%)	-	10 (34.5%)	0.621[e]	0.06[g]
Reported by teachers, n (%) (N=58)	-	11 (35.5%)	-	13 (48.2%)	0.329[e]	0.13[g]
Sports enjoyment[b] - Adjusted GEQ total score						
Reported by mothers (N=82)	27.27 ± 3.67	27.13 ± 3.74	28.27 ± 2.83	28.29 ± 2.42	0.882[c]	0.37[f]
Reported by fathers (N=73)	27.24 ± 2.64	26.44 ± 3.86	27.48 ± 3.21	27.79 ± 3.09	0.017[c]	0.39[f]
Reported by teachers (N=56)	-	27.40 ± 4.24	-	28.23 ± 2.69	0.394[d]	0.23[f]
Sports participation and enjoyment reported by child						
Sports enjoyment[b] (N=86)	1.55 ± 0.73	1.57 ± 0.70	1.62 ± 0.89	1.42 ± 0.76	0.158[c]	0.21[f]
Sports participation per week (N=86)	2.45 ± 1.47	2.86 ± 1.49	2.43 ± 2.13	2.45 ± 1.45	0.453[c]	0.28[f]

Values are mean ± SD, unless otherwise specified.
[a] A higher score indicates more problems or poorer functioning.
[b] A higher score indicates less problems or better functioning.
[c] GEE analysis. *P*-value indicates the level of significance of the interaction between condition and follow-up time.
[d] T-test.
[e] Chi-square test.
[f] Cohen's $d = (M_{CHIP\_T2} - M_{CAU\_T2})/SD_{pooled}$. $SD_{pooled} = \sqrt{((SD_{CHIP\_T2}{}^2 + SD_{CAU\_T2}{}^2) / 2)}$.
[g] Phi coefficient.

Table 4 Parental and family outcomes.

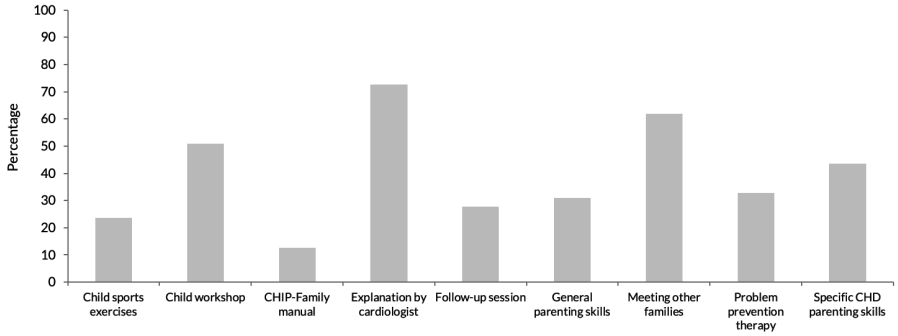
	Intervention group (N = 47)		Control group (N = 43)			
Outcome measure	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	***P*-value**	**Cohen's *d***
Parental mental health[a] - SCL-90-R total score						
Mothers (N=87)	129.02 ± 41.97	125.98 ± 41.97	117.59 ± 22.18	115.83 ± 23.109	0.922	0.30
Fathers (N=76)	106.12 ± 16.08	102.06 ± 16.90	119.65 ± 44.05	108.20 ± 22.52	0.309	0.31
Parental worry[a] - PSWQ total score						
Mothers (N=83)	45.15 ± 13.67	44.66 ± 13.27	42.47 ± 11.04	42.63 ± 9.88	0.864	0.17
Fathers (N=73)	36.34 ± 8.45	35.90 ± 9.86	36.64 ± 11.96	35.24 ± 10.69	0.515	0.06
Parental stress[a] - NOSIK total score						
Mothers (N=79)	51.82 ± 25.83	52.50 ± 25.67	48.39 ± 20.87	47.47 ± 19.43	0.325	0.22
Fathers (N=69)	45.25 ± 19.85	42.59 ± 18.84	40.04 ± 15.02	39.52 ± 17.03	0.437	0.17
Parental stress[a] - DT-P thermometer						
Mothers (N=79)	3.78 ± 2.79	3.66 ± 2.86	4.03 ± 3.21	2.71 ± 2.71	0.143	0.34
Fathers (N=69)	1.97 ± 2.15	1.28 ± 1.49	2.40 ± 2.60	2.67 ± 2.60	0.049	0.66
Parental stress[a] - DT-P total score						
Mothers (N=79)	7.75 ± 6.49	7.49 ± 7.89	7.89 ± 6.17	5.24 ± 5.53	0.006	0.33
Fathers (N=69)	3.16 ± 6.31	2.52 ± 4.48	4.04 ± 4.69	4.15 ± 5.80	0.054	0.31
Parental quality of life[b] - SF-36 Mental component score						
Mothers (N=80)	48.63 ± 9.71	48.09 ± 10.99	49.58 ± 9.37	50.19 ± 7.35	0.402	0.22
Fathers (N=70)	53.93 ± 4.27	54.57 ± 2.62	51.98 ± 6.48	53.12 ± 4.09	0.747	0.42

Table 4 Continued

	Intervention group (N = 47)		Control group (N = 43)			
Outcome measure	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	***P*-value**	**Cohen's *d***
Parental quality of life[b] - SF-36 Physical component score						
Mothers (N=80)	51.50 ± 8.52	53.51 ± 6.99	52.27 ± 6.54	53.49 ± 5.55	0.812	0.003
Fathers (N=70)	54.18 ± 5.38	54.18 ± 4.66	52.36 ± 5.98	52.24 ± 7.41	0.793	0.31
General family functioning[a] - FAD						
Reported by mothers (N=83)	1.57 ± 0.43	1.59 ± 0.51	1.49 ± 0.42	1.49 ± 0.50	0.628	0.20
Reported by fathers (N=71)	1.50 ± 0.49	1.41 ± 0.37	1.56 ± 0.41	1.55 ± 0.41	0.960	0.36
Disease-specific knowledge[c]						
Reported by mothers (N=82)	5.53 ± 3.69	7.84 ± 3.05	5.69 ± 3.89	7.00 ± 3.57	0.302	0.25
Reported by fathers (N=75)	4.66 ± 3.32	6.38 ± 3.67	5.30 ± 3.11	6.14 ± 3.48	0.037	0.07

Values are mean ± SD. P-values indicate the level of significance of the interaction between condition and follow-up time.
[a] A higher score indicates more problems or poorer functioning.
[b] A higher score indicates less problems or better functioning.
[c] A higher score indicates more disease-specific knowledge (maximum score = 14).

Figure 2 Parents' ratings of most useful components of the CHIP-Family intervention (multiple answers possible).



Following the results of the present study, we were interested in considering differences between CHIP-Family and the previous CHIP-School on which it was based, and what these might tell us about future interventions and evaluations. Two classes of differences may be important:

· The intervention – Some key differences may have been important. Firstly, as noted above, CHIP-School comprised a behavioral experiment – the bicycle exercise test – to directly challenge assumptions about fragility and poor exercise capacity. For logistical reasons, ours did not. CHIP-School authors noted that parents had rated this component as the most helpful (personal communication). Secondly, we incorporated parallel workshops for children and siblings. Whilst theoretically we expected this to enhance impact, having their children attend the same day may in fact have diluted the importance of, and engagement with, the primacy of the parent focus of the intervention. It should be noted, however, that parents did rate the child workshop positively. Finally, we had smaller groups of parents (three to five) compared to CHIP-School. Again, we expected this to enhance impact, but such may also have moderated the social facilitation and support impact of the groups.

· The sample – In CHIP-Family we had lower rates of uptake (24%) compared to CHIP-School (60%). Although our responders seemed similar to non-responders (see above) on CHD severity measures, our samples may have differed on other important psychosocial ways which our studies are not able to compare but which relate to the issue of targeting such interventions. It is difficult to draw clear conclusions here, but this merits consideration in future research. CHIP-School targeted families just before the child made the transition to school, whereas

CHIP-Family included families of children who had already started school. Drotar [67] makes the case for timing of early interventions at the cusp of developmental transitions and this may be important.

As CHIP-Family was designed as a preventive intervention, patients and their families were not selected for participation in the RCT based on their level of psychosocial difficulties. Considering the baseline scores, participants seemed to be functioning relatively well. That is, compared with the general population, all mean scores fell within the normal range. One might expect that baseline scores would have been higher if we would have only included children with severe or complex CHD. However, a meta-analysis [8] has shown that disease severity in children with CHD is not related to internalizing, externalizing, and overall emotional and behavioral problems. Also, the majority of parents were highly educated. Significant improvements might have been found if we provided CHIP-Family specifically to patients and families who suffered from clinically significant psychosocial difficulties.

Moreover, besides issues related to early childhood, several topics were discussed in the CHIP-Family intervention concerning future issues related to adolescence and young adulthood, such as alcohol use, smoking, sexuality, insurances, and career possibilities. This was done to provide parents an overall future perspective and also to encourage parents to ask for advice or help from the medical staff. Furthermore, these were topics often addressed by parents during the intervention. Whether this kind of psychoeducation has positive effects when these children reach adolescence could not be assessed within the shorter 6-month follow-up period.

Remarkably, although no differences in participant characteristics were found between the CHIP-Family and the care as usual group, a baseline difference was found in child emotional and behavioral problems reported by mothers. Mothers in the CHIP-Family group reported more child emotional and behavioral problems than mothers in the care as usual group. This might be explained by the fact that participants were aware of randomization outcome prior to baseline assessment. Due to logistical reasons, this could not be arranged otherwise. Parents might have psychologically prepared for the CHIP-Family intervention by reflecting on questions they wanted to discuss, which may have increased their awareness of problems and, consequently, increased their problem reports.

Moreover, we found that both mother-reports and father-reports of the CBCL questionnaire in the CAU and CHIP-Family group improved similarly over time. This might be explained by the "question-behavior effect". That is, behavior of participants can be affected by merely filling out questionnaires [68], which was done by parents of children in both the CAU and the CHIP-Family group. Furthermore, the information letters sent to potential participants contained information on common psychosocial issues in young children with CHD. Reading this information may have had a normalizing effect. Also, perhaps the feeling of receiving more attention from the hospital staff by participating in the study may have contributed to positive outcomes for both groups

Interestingly, we found that parents of children with less severe CHD rated usefulness of and satisfaction with the child workshop more favorably than parents of children with more severe CHD. This could be attributed to the fact that children with less severe CHD have less outpatient clinic visits compared to children with more severe CHD. Parents of children who make less clinic visits might appreciate the attention of health care professionals more compared to parents of children who are accustomed to more frequent visits to clinic. Alternatively, parents of children with more severe CHD might prefer a different child intervention program than parents of children with less severe CHD.

Strengths and limitations

This study has several strengths. Worldwide, CHIP-Family is the first psychosocial intervention for children with CHD that is comprised of both a specific child and parent module. Protocol adherence was strong. Moreover, fathers are underrepresented in pediatric research and, when fathers are included, mothers' and fathers' reports often are not analyzed separately [69, 70]. Both mothers and fathers participated in CHIP-Family and their outcome reports were analyzed separately.

A number of limitations should also be considered. Firstly, as mentioned above, informing participants of randomization outcome prior to the baseline assessment may have influenced the results. Secondly, due to the nature of the intervention, it was not possible to blind participants for group status. Thirdly, the differences in outcome scores in favor of the CHIP-Family group might have been statistically significant if the sample size would have been larger. Finally, perhaps we would have found larger effects if we had used more disease-specific questionnaires related to

family functioning and worry. However, at the start of this study, these tools were not available in Dutch.

Conclusion

In summary, CHIP-Family was evaluated positively by participants and seems to meet parents' and patients' needs. However, the intervention did not significantly improve the psychosocial well-being of young children with CHD and their families at 6-month follow-up. As CHIP-Family did not meet its expectations, future research should focus on which patients and families will benefit most from a psychosocial intervention. Future research should also examine whether intervention programs should be adjusted according to CHD severity. Moreover, alternative formats in which psychosocial interventions may be provided could be considered, such as easily accessible online psychoeducation or group videoconferences. Also, psychosocial topics could be integrated into shared medical appointments [71], which show promising results.

ACKNOWLEDGEMENTS

We are grateful to all families that participated in this trial and thank the Dutch Patient Association for Congenital Heart Disease for their advice and their help in facilitating the conduct of this trial. We also thank all psychologists, pediatric cardiologists, physiotherapists, and master's students for their efforts in providing the CHIP-Family intervention.

FINANCIAL SUPPORT

This work was supported by Fonds NutsOhra, Amsterdam, the Netherlands (grant number 101.083). The funding source had no role in the design of the study, its execution, analysis, interpretation of the data, or decision to submit results.

CONFLICTS OF INTEREST

None.

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by Medical Ethics Committee of the Erasmus Medical Center. Informed consent was obtained from all patients in accordance with the university hospital policies.

REFERENCES

1. Torowicz D, Irving SY, Hanlon AL, Fullbright Sumpter D and Medoff-Cooper B. Infant temperament and parent stress in 3 month old infants following surgery for complex congenital heart disease. J Dev Behav Pediatr. 2010; 31: 202-8.
2. Solberg O, Dale MT, Holmstrom H, Eskedal LT, Landolt MA and Vollrath ME. Emotional reactivity in infants with congenital heart defects and maternal symptoms of postnatal depression. Arch Womens Ment Health. 2011; 14: 487-92.
3. Brosig CL, Mussatto KA, Kuhn EM and Tweddell JS. Psychosocial outcomes for preschool children and families after surgery for complex congenital heart disease. Pediatr Cardiol. 2007; 28: 255-62.
4. Bellinger DC, Newburger JW, Wypij D, Kuban KC, duPlesssis AJ and Rappaport LA. Behaviour at eight years in children with surgically corrected transposition: The Boston Circulatory Arrest Trial. Cardiol Young. 2009; 19: 86-97.
5. Martinez-Biarge M, Jowett VC, Cowan FM and Wusthoff CJ. Neurodevelopmental outcome in children with congenital heart disease. Semin Fetal Neonatal Med. 2013; 18: 279-285.
6. Puosi R, Korkman M, Sarajuuri A et al. Neurocognitive development and behavioral outcome of 2-year-old children with univentricular heart. J Int Neuropsychol Soc. 2011; 17: 1094-103.
7. Hovels-Gurich HH, Konrad K, Skorzenski D et al. Long-term behavior and quality of life after corrective cardiac surgery in infancy for tetralogy of Fallot or ventricular septal defect. Pediatr Cardiol. 2007; 28: 346-54.
8. Karsdorp PA, Everaerd W, Kindt M and Mulder BJ. Psychological and cognitive functioning in children and adolescents with congenital heart disease: a meta-analysis. J Pediatr Psychol. 2007; 32: 527-41.
9. McCusker CG, Armstrong MP, Mullen M, Doherty NN and Casey FA. A sibling-controlled, prospective study of outcomes at home and school in children with severe congenital heart disease. Cardiol Young. 2013; 23: 507-16.
10. Calderon J, Bonnet D, Pinabiaux C, Jambaque I and Angeard N. Use of early remedial services in children with transposition of the great arteries. J Pediatr. 2013; 163: 1105-10.
11. Riehle-Colarusso T, Autry A, Razzaghi H et al. Congenital Heart Defects and Receipt of Special Education Services. Pediatrics. 2015; 136: 496-504.
12. Gerstle M, Beebe DW, Drotar D, Cassedy A and Marino BS. Executive functioning and school performance among pediatric survivors of complex congenital heart disease. J Pediatr. 2016; 173: 154-9.
13. Shillingford AJ, Glanzman MM, Ittenbach RF, Clancy RR, Gaynor JW and Wernovsky G. Inattention, hyperactivity, and school performance in a population of school-age children with complex congenital heart disease. Pediatrics. 2008; 121: 759-67.

14. Farr SL, Downing KF, Riehle-Colarusso T and Abarbanell G. Functional limitations and educational needs among children and adolescents with heart disease. Congenit Heart Dis 2018; 13: 633-9.

15. Bellinger DC, Wypij D, duPlessis AJ et al. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: the Boston Circulatory Arrest Trial. J Thorac Cardiovasc Surg. 2003; 126: 1385-96.

16. Cassidy AR, Ilardi D, Bowen SR et al. Congenital heart disease: A primer for the pediatric neuropsychologist. Child Neuropsychol. 2017: 1-44.

17. Spijkerboer AW, Utens EM, Bogers AJ, Helbing WA and Verhulst FC. A historical comparison of long-term behavioral and emotional outcomes in children and adolescents after invasive treatment for congenital heart disease. J Pediatr Surg. 2008; 43: 534-9.

18. Ringle ML and Wernovsky G. Functional, quality of life, and neurodevelopmental outcomes after congenital cardiac surgery. Semin Perinatol. 2016; 40: 556-70.

19. Bellinger DC and Newburger JW. Neuropsychological, psychosocial, and quality-of-life outcomes in children and adolescents with congenital heart disease. Progr Pediatr Cardiol. 2010; 29: 87-92.

20. Schaefer C, von Rhein M, Knirsch W et al. Neurodevelopmental outcome, psychological adjustment, and quality of life in adolescents with congenital heart disease. Dev Med Child Neurol. 2013; 55: 1143-9.

21. Kovacs AH and Moons P. Psychosocial functioning and quality of life in adults with congenital heart disease and heart failure. Heart Fail Clin. 2014; 10: 35-42.

22. Holbein CE, Fogleman ND, Hommel K et al. A multinational observational investigation of illness perceptions and quality of life among patients with a Fontan circulation. Congenit Heart Dis. 2018; 13: 392-400.

23. McCrindle BW, Williams RV, Mital S et al. Physical activity levels in children and adolescents are reduced after the Fontan procedure, independent of exercise capacity, and are associated with lower perceived general health. Arch Dis Child. 2007; 92: 509-14.

24. Massin MM, Hovels-Gurich HH, Gerard P and Seghaye MC. Physical activity patterns of children after neonatal arterial switch operation. Ann Thorac Surg. 2006; 81: 665-70.

25. Dulfer K, Helbing WA, Duppen N and Utens EM. Associations between exercise capacity, physical activity, and psychosocial functioning in children with congenital heart disease: a systematic review. Eur J Prev Cardiol. 2014; 21: 1200-15.

26. Duppen N, Takken T, Hopman MT et al. Systematic review of the effects of physical exercise training programmes in children and young adults with congenital heart disease. Int J Cardiol. 2013; 168: 1779-87.

27. Voss C, Duncombe SL, Dean PH, de Souza AM and Harris KC. Physical Activity and Sedentary Behavior in Children With Congenital Heart Disease. J Am Heart Assoc. 2017; 6.

28. Casey FA, Stewart M, McCusker CG et al. Examination of the physical and psychosocial determinants of health behaviour in 4-5-year-old children with congenital cardiac disease. Cardiol Young. 2010; 20: 532-7.

29. McCusker CG, Doherty NN, Molloy B et al. Determinants of neuropsychological and behavioural outcomes in early childhood survivors of congenital heart disease. Arch Dis Child. 2007; 92: 137-41.

30. Woolf-King SE, Anger A, Arnold EA, Weiss SJ and Teitel D. Mental Health Among Parents of Children With Critical Congenital Heart Defects: A Systematic Review. J Am Heart Assoc. 2017; 6.

31. Kolaitis GA, Meentken MG and Utens E. Mental Health Problems in Parents of Children with Congenital Heart Disease. Front Pediatr. 2017; 5: 102.

32. McClung N, Glidewell J and Farr SL. Financial burdens and mental health needs in families of children with congenital heart disease. Congenit Heart Dis. 2018; 13: 554-62.

33. Lesch W, Specht K, Lux A, Frey M, Utens E and Bauer U. Disease-specific knowledge and information preferences of young patients with congenital heart disease. Cardiol Young. 2014; 24: 321-30.

34. Levert EM, Helbing WA, Dulfer K, van Domburg RT and Utens EM. Psychosocial needs of children undergoing an invasive procedure for a CHD and their parents. Cardiol Young 2017; 27: 243-54.

35. Tesson S, Butow PN, Sholler GF, Sharpe L, Kovacs AH and Kasparian NA. Psychological interventions for people affected by childhood-onset heart disease: A systematic review. Health Psychol. 2019; 38: 151-61.

36. McCusker CG, Doherty NN, Molloy B et al. A randomized controlled trial of interventions to promote adjustment in children with congenital heart disease entering school and their families. J Pediatr Psychol. 2012; 37: 1089-103.

37. Thompson RJ, Jr., Gustafson KE, Hamlett KW and Spock A. Stress, coping, and family functioning in the psychological adjustment of mothers of children and adolescents with cystic fibrosis. J Pediatr Psychol. 1992; 17: 573-85.

38. van der Mheen M, van Beynum IM, Dulfer K et al. The CHIP-Family study to improve the psychosocial wellbeing of young children with congenital heart disease and their families: design of a randomized controlled trial. BMC Pediatr 2018; 18: 230.

39. Saigal S and Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008; 371: 261-9.

40. Hoffman JI and Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002; 39: 1890-900.

41. Utens E, Dulfer K, Legerstee J, Van Beynum I, Meentken M, van der Mheen M. Dutch translation of: Beyond the Diagnosis: Family Adaptation to Congenital Heart Disease. Erasmus MC - Sophia Children's Hospital, Rotterdam; 2016.

42. Utens EMWJ. FIJN: VRIENDEN! Handleiding voor ouders om emotionele veerkracht door middel van spel op te bouwen bij 4 tot en met 7 jarigen. Erasmus MC - Sophia Kinderziekenhuis, Rotterdam; 2011.

43. Barrett PM. Fun FRIENDS: The teaching and training manual for group leaders. Fun FRIENDS Publishing, Brisbane; 2007.

44. Dulfer K, Duppen N, Kuipers IM et al. Aerobic exercise influences quality of life of children and youngsters with congenital heart disease: a randomized controlled trial. J Adolesc Health. 2014; 55: 65-72.

45. Utens E and Dulfer K. Rotterdams Kwaliteit van Leven Interview; 2010.

46. Achenbach TM and Rescorla LA. Manual for the ASEBA school-age forms & profiles. University of Vermont, Research Center for Children, Youth, & Families, Burlington, Vermont; 2001.

47. Verhulst FC and van der Ende J. Handleiding ASEBA Vragenlijsten voor leeftijden 6 tot en met 18 jaar. ASEBA, Rotterdam, The Netherlands; 2013.

48. Smidts DP and Huizinga M. BRIEF Executieve Functies Gedragsvragenlijst: Handleiding. Hogrefe Uitgevers, Amsterdam; 2009.

49. Van der Heijden KB, Suurland J, De Sonneville LMJ and Swaab HJT. BRIEF-P Vragenlijst executieve functies voor 2- tot 5-jarigen. Hogrefe uitgevers, Amsterdam; 2013.

50. Langraf JM, Abetz L and Ware JE. The CHQ user's manual. Health Act, Boston; 1999.

51. Stevens M, Moget P, de Greef MH, Lemmink KA and Rispens P. The Groningen Enjoyment Questionnaire: a measure of enjoyment in leisure-time physical activity. Percept Mot Skills. 2000; 90: 601-4.

52. Dulfer K, Duppen N, Blom NA et al. Effect of exercise training on sports enjoyment and leisure-time spending in adolescents with complex congenital heart disease: the moderating effect of health behavior and disease knowledge. Congenit Heart Dis. 2014; 9: 415-23.

53. Arrindell WA and Ettema JHM. SCL-90. Symptom Checklist. Handleiding bij een multidimensionele psychopathologie-indicator. Swets Test Publishers, Lisse; 2003.

54. Meyer TJ, Miller ML, Metzger RL and Borkovec TD. Development and validation of the Penn State Worry Questionnaire. Behav Res Ther. 1990; 28: 487-95.

55. Van der Heiden C, Muris P, Bos AE and Van der Molen HT. Factor structure of the Dutch version of the Penn State Worry Questionnaire. Journal of Behavior Therapy and Experimental Psychiatry. 2010; 41: 304-9.

56. De Brock AJLL, Vermulst AA, Gerris JRM and Abidin RR. NOSI: Nijmeegse Ouderlijke Stress Index, handleiding experimentele versie. Pearson; 1992.

57. Haverman L, van Oers HA, Limperg PF et al. Development and validation of the distress thermometer for parents of a chronically ill child. J Pediatr. 2013; 163: 1140-6.

58. Aaronson NK, Muller M, Cohen PD et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol. 1998; 51: 1055-68.

59. Epstein NB, Baldwin LM and Bishop DS. The McMaster Family Assessment Device. J Marital Fam Ther. 1983; 9: 171-180.

60. Utens EMWJ and Dulfer K. Rotterdam Knowledge Questionnaire; 2010.

61. Zeger SL, Liang KY and Albert PS. Models for longitudinal data: a generalized estimating equation approach. Biometrics. 1988; 44: 1049-1060.

62. Twisk JW. Longitudinal data analysis. A comparison between generalized estimating equations and random coefficient analysis. Eur J Epidemiol. 2004; 19: 769-776.

63. Corp I. IBM SPSS Statistics for Windows. IBM Corp, Armonk, NY; 2016.

64. Hughes B. Psychology in Crisis. Macmillian International Higher Education; 2018.

65. Stehl ML, Kazak AE, Alderfer MA et al. Conducting a randomized clinical trial of an psychological intervention for parents/caregivers of children with cancer shortly after diagnosis. J Pediatr Psychol. 2009; 34: 803-16.

66. Law EF, Fisher E, Fales J, Noel M and Eccleston C. Systematic review and meta-analysis of parent and family-based interventions for children and adolescents with chronic medical conditions. J Pediatr Psychol. 2014; 39: 866-86.

67. Drotar D. Psychological interventions in childhood chronic illness. American psychological Association, Washington DC; 2006.

68. Wilding S, Conner M, Sandberg T et al. The question-behaviour effect: A theoretical and methodological review and meta-analysis. Eur Rev Soc Psychol. 2016; 27: 196-230.

69. Phares V, Lopez E, Fields S, Kamboukos D and Duhig AM. Are fathers involved in pediatric psychology research and treatment? J Pediatr Psychol. 2005; 30: 631-43.

70. Parent J, Forehand R, Pomerantz H, Peisch V and Seehuus M. Father Participation in Child Psychopathology Research. J Abnorm Child Psychol. 2017; 45: 1259-70.

71. Kirsh SR, Aron DC, Johnson KD et al. A realist review of shared medical appointments: How, for whom, and under what circumstances do they work? BMC Health Serv Res. 2017; 17: 113.

5

CHAPTER 5

Emotional and behavioral problems in children with dilated cardiomyopathy

Malindi van der Mheen, Marijke H. van der Meulen, Susanna L. den Boer, Dayenne J. Schreutelkamp, Jan van der Ende, Pieter F.A. de Nijs, Johannes M.P.J. Breur, Ronald B. Tanke, Nico A. Blom, Lukas A.J. Rammeloo, Arend D.J. ten Harkel, Gideon J. du Marchie Sarvaas, Elisabeth M.W.J. Utens*, Michiel Dalinghaus*

*These authors share senior authorship.

European Journal of Cardiovascular Nursing, 2019, advance online publication

ABSTRACT

Background. Dilated cardiomyopathy (DCM) in children is an important cause of severe heart failure and carries a poor prognosis. Adults with heart failure are at increased risk of anxiety and depression and such symptoms predict adverse clinical outcomes such as mortality. In children with DCM, studies examining these associations are scarce.

Aims. We studied whether in children with DCM: (1) the level of emotional and behavioral problems was increased as compared to normative data, and (2) depressive and anxiety problems were associated with the combined risk of death or cardiac transplantation.

Methods. To assess emotional and behavioral problems in children with DCM, parents of 68 children, aged 1.5-18 years (6.9±5.7 years) completed the Child Behavior Checklist.

Results. Compared to normative data, more young children (1.5-5 years) with DCM had somatic complaints (24.3% vs. 8.0%; $p < .001$), but fewer had externalizing problems (5.4% vs. 17.0%; $p = .049$). Overall internalizing problems did not reach significance. Compared to normative data, more older children (6-18 years) showed internalizing problems (38.7% vs. 17.0%; $p = .001$), including depressive (29.0% vs. 8.0%; $p < .001$) and anxiety problems (19.4% vs. 8.0%; $p = .023$), and somatic complaints (29.0% vs. 8.0%; $p < .001$). Anxiety and depressive problems, corrected for heart failure severity, did not predict the risk of death or cardiac transplantation.

Conclusion. Children of 6 years and older showed more depressive and anxiety problems than the normative population. Moreover, in both age groups, somatic problems were common. No association with outcome could be demonstrated.

INTRODUCTION

Cardiomyopathies are disorders characterized by structural and functional abnormalities of the heart. The most common subtype in children is dilated cardiomyopathy (DCM), accounting for approximately 60% of pediatric cardiomyopathies [1, 2]. DCM, which is characterized by impaired systolic function and dilation of the left ventricle [3], is estimated to affect 0.57 per 100,000 children annually [4]. Though disease presentation can vary greatly, 80% of patients show symptoms related to heart failure, such as fatigue, orthopnea, edema, and excessive sweating. Symptoms can also include circulatory collapse, arrhythmias, thromboembolic events, and sudden death [5]. Although some children recover [6], the prognosis of DCM generally is poor: within 2 years after diagnosis, approximately 40% of children die or undergo cardiac transplantation [4, 6-8], making DCM the leading indication for cardiac transplantation worldwide [9-11]. Considering the symptoms and prognosis of DCM, substantial effects on psychosocial wellbeing can be expected [12].

Compelling evidence from two meta-analyses shows that adults with heart failure are at increased risk of anxiety and depression [13, 14]. Few studies have examined the psychosocial wellbeing of children with DCM, but, indeed, it has been found that children with DCM have a lower health-related quality of life (HRQoL) than healthy children [12, 15-18]. However, studies examining emotional and behavioral problems in children with DCM are scarce. Moreover, the currently available studies have small sample sizes ($n \leq 15$) and show contradictory results. In a cross-sectional study, half ($n = 6$ out of 12) of children with cardiomyopathy listed for cardiac transplantation showed clinically significant overall emotional and behavioral problems [19]. In contrast, a study examining depressive symptoms in children with DCM ($n = 15$) did not find higher rates of symptoms compared with healthy children [20]. However, it should be noted that these studies used different questionnaires.

Regarding the impact of impaired HRQoL on cardiac outcomes, two studies have shown that children's physical HRQoL (reported by parents) predicts mortality and cardiac transplantation, independent from heart failure severity [15, 17]. Also, a meta-analysis [13] and reviews [21, 22] have consistently found that depressive and anxiety symptoms in adults with heart failure predict mortality and other adverse clinical outcomes, such as hospitalization and arrhythmias. However, to the best of our knowledge, the predictive value of depressive and anxiety symptoms in

children with DCM has not been previously studied. Information on the predictive value of depressive and anxiety symptoms may be valuable for clinical management strategies. Depressive and anxiety problems may lead to poorer self-care and, in turn, to disease progression [22].

The aim of the present study was twofold: firstly, we evaluated the level of parent-reported emotional and behavioral problems in children with DCM compared with the general population. Secondly, we exploratively examined whether the level of parent-reported anxiety and depressive problems predicted the combined risk of death and cardiac transplantation whilst controlling for heart failure severity. Based on the aforementioned adult studies, we hypothesized that children with DCM would show more anxiety and depressive problems than children in the general population. Moreover, we hypothesized that anxiety and depressive problems would predict mortality in children with DCM independent from heart failure severity.

METHODS

All data used in this observational, cross-sectional study were derived from a larger multicenter longitudinal study in children with heart failure secondary to cardiomyopathy [15]. The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center (protocol number NL45663.078) and by the institutional review boards of all participating centers. The study performed conformed to the ethical guidelines of the Declaration of Helsinki [23] and reported following the STROBE statement. Before participation, written informed consent was obtained from all patients' parents or legal guardians and from all patients aged 12 years or above.

Participants

Participants were recruited from 1 October 2010 to 1 November 2015 through seven tertiary centers for pediatric cardiology in the Netherlands. The database was closed on 1 July 2017. Children were eligible to participate if they had heart failure secondary to DCM. DCM was defined as fractional shortening ≤25% and left ventricular end-diastolic dimension z-score >2 for body surface area. DCM could be idiopathic or secondary to other causes. Exclusion criteria were known mental retardation, congenital heart disease, neuromuscular disease, and insufficient mastery of the Dutch language by parents. In the current study, we only included 1.5-18-year-old children due to age restrictions of the used questionnaire. Since

age and gender-matched normative data on emotional and behavioral problems is available, we did not recruit a healthy control group [24].

Procedure

Children were either included at DCM diagnosis or were included at an outpatient appointment for a previously diagnosed DCM in one of the participating tertiary pediatric cardiology centers. Demographic variables were obtained at inclusion. Socioeconomic status was based on the highest of both parents' occupations and categorized into low, low to middle, middle, or high according to the international classification system [25]. Parents were asked to complete a questionnaire assessing their child's emotional and behavioral problems during an outpatient clinic visit. During the same visit, a pediatric cardiologist completed the New York University Pediatric Heart Failure Index (NYU PHFI) [26]. This validated index assesses heart failure severity based on symptoms and medication use. Scores range from 0 to 30. A higher score indicates more severe heart failure.

Emotional and behavioral problems

One of each participant's parents completed the problem section of the Child Behavior Checklist (CBCL) [27]. Depending on the child's age, the CBCL 1½-5 (100 items; children aged 1.5-5 years) or the CBCL/6-18 (120 items; children aged 6-18 years) was completed. For both versions, response categories range from 0 (not true) to 2 (very true or often true). The CBCL assesses overall emotional and behavioral problems and specific aspects of mental health and problem behavior. In addition to an overall total problem score, broadband scale scores can be calculated for Externalizing Problems (i.e., externally directed problems affecting the environment, such as aggression and delinquency) and Internalizing Problems (i.e., internally directed problems such as depression, anxiety, and somatic complaints). Furthermore, the CBCL 1½-5 consists of five scales based on the fifth edition of the Diagnostic and Statistical Manual Of Mental Disorders (DSM-5; i.e., Depressive Problems, Anxiety Problems, Attention Deficit/Hyperactivity Problems, Oppositional Defiant Problems, and Autism Spectrum Problems). In addition, seven empirical scales can be calculated (i.e., Anxious/Depressed, Somatic Complaints, Attention Problems, Aggressive Behavior, Emotionally Reactive, Withdrawn, and Sleep Problems). The CBCL/6-18 consists of six DSM-5 based scales (i.e., Depressive Symptoms, Anxiety Problems, Somatic Problems, Attention Deficit/Hyperactivity Problems, Oppositional Defiant Problems, and Conduct Problems) and 8 empirical scales (i.e., Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems,

Rule-Breaking Behavior, and Aggressive Behavior). On all scales, higher scores indicate more problems. For each scale, scores can be interpreted as falling in the normal, borderline, or clinical range by comparing scale scores with norm data. Scores in the borderline or clinical range indicate psychopathological problems with a need for clinical follow-up and/or intervention. The CBCL has adequate psychometric properties and normative data from the Dutch general population are available [24].

Endpoint

We used a combined endpoint of death and cardiac transplantation. Information on mortality and cardiac transplantation was retrieved from patient records. Follow-up was censored at July 1, 2017.

Statistical analyses

Firstly, we examined whether the proportion of children scoring in the borderline or clinical range of emotional and behavioral problems was larger in our DCM study population than in the general population. All raw scale scores were converted to percentiles using the Achenbach System of Empirically Based Assessment Standard norm data, which is based on data of Dutch children from the general population and accounts for age and gender [27]. Conforming with the CBCL manual [27], for the Total Problems scale, Internalizing Problems scale, and Externalizing Problems scale, percentile scores of 83 or lower were defined as non-clinical and percentile scores of 84 or higher were defined as borderline/clinical. For the DSM scales and empirical scales, percentile scores of 92 or lower were defined as non-clinical and percentile scores of 93 or higher were defined as borderline/clinical. One sample binomial tests were conducted for each scale of the CBCL 1½-5 and the CBCL/6-18 to test whether the proportion of children with DCM scoring in the borderline/clinical range was higher than the proportion in the norm group.

Secondly, we conducted a Cox regression analysis to examine whether anxiety and depressive problems predicted the combined endpoint of death and cardiac transplantation whilst controlling for heart failure severity. The covariates entered into the model were the CBCL scale scores for Anxiety Problems and Depressive Problems and the NYU PHFI. We used t-scores to account for differences between the two versions of the CBCL (i.e., CBCL/1½-5 and CBCL/6-18) Anxiety Problems and Depressive Problems scale scores. The NYU PHFI was added to the model because heart failure severity is a known predictor of mortality [15]. All analyses were performed using SPSS Statistics version 24.0 [28].

RESULTS

In total, 144 children with DCM participated in the larger multicenter longitudinal study in children with heart failure secondary to cardiomyopathy from which data for the current study was derived. Of this group, 52 children were excluded from participation in the current study (N = 26 had a too short follow-up period to fill out the CBCL, N = 14 were younger than 1.5 years, N = 7 had a neuromuscular disease, N = 5 did not master the Dutch language sufficiently). Therefore, 92 children met the eligibility criteria for the current study, 68 of whom consented to participate in the current study (see Figure 1). Participant characteristics are presented in Table 1.

Figure 1 Participation flowchart.

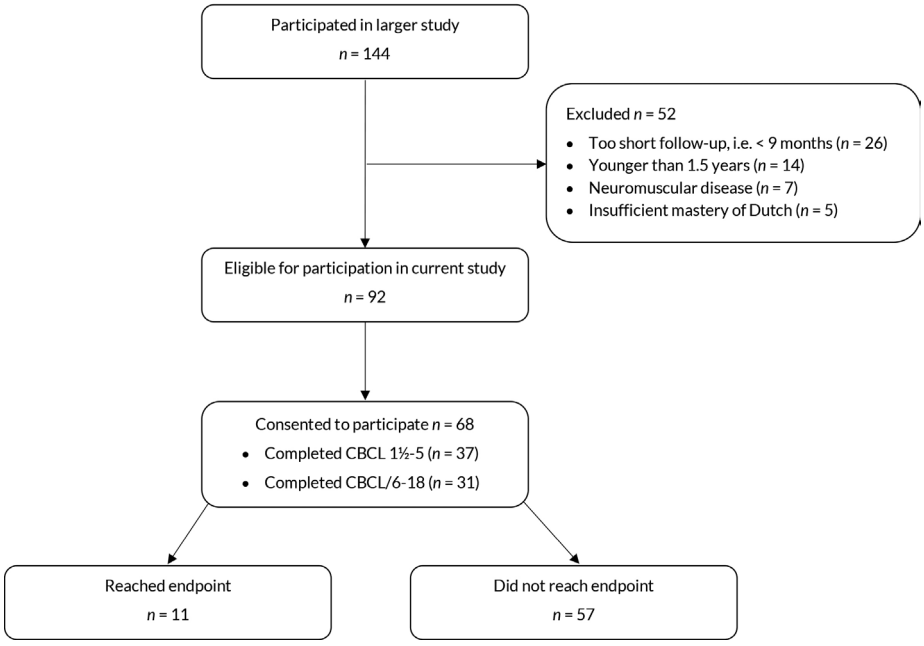


Table 1 Participant characteristics.

Characteristic	Overall group (*n*=68)		Did not reach endpoint (*n*=57)		Reached endpoint (*n*=11)	
	1.5-5 years (*n*=37)	6-18 years (*n*=31)	1.5-5 years (*n*=31)	6-18 years (*n*=26)	1.5-5 years (*n*=6)	6-18 years (*n*=5)
Male gender, *n* (%)	20 (54.1%)	17 (54.8%)	18 (58.1%)	16 (61.5%)	2 (33.3%)	1 (20.0%)
Age in years, *M* (*SD*)	2.2 (1.3)	12.4 (3.5)	2.0 (0.5)	12.5 (3.6)	3.3 (1.2)	11.8 (3.4)
Time since DCM diagnosis in months, median (IQR*)	19.0 (12.0-36.0)	57.0 (24.0-107.0)	18.0 (12.0-24.0)	58.5 (27.0-110.0)	40.5 (24.5-59.0)	24.0 (17.0-73.5)
NYU PHFI†, *M* (*SD*)	6.3 (4.8)	7.2 (3.8)	4.8 (3.2)	5.5 (3.1)	14.2 (3.9)	12.6 (2.1)
Socioeconomic status‡, *n* (%)						
Low	1 (2.7%)	2 (6.5%)	1 (3.2%)	2 (7.7%)	0 (0.0%)	0 (0.0%)
Low to middle	10 (27.0%)	10 (32.3%)	8 (25.8%)	10 (38.5%)	2 (33.3%)	0 (0.0%)
Middle	3 (8.1%)	6 (19.4%)	3 (9.7%)	6 (23.1%)	0 (0.0%)	0 (0.0%)
High	16 (43.2%)	10 (32.3%)	13 (41.9%)	5 (19.2%)	3 (50.0%)	5 (100.0%)
Missing	7 (18.9%)	3 (9.7%)	6 (19.4%)	3 (11.5%)	1 (16.7%)	0 (0.0%)

* IQR = Interquartile range.
† NYU PHFI = New York University Pediatric Heart Failure Index.
‡ SES was determined by parents' occupation level [25].

Emotional and behavioral problems compared with the general population

1.5- to 5-year-old children (CBCL 1½-5)

The proportion of parent-reported emotional and behavioral problems in 1.5- to 5-year-old children with DCM and children in the norm group is shown in Table 2. The CBCL 1½-5 was completed for 37 participants (by N = 9 fathers, N = 25 mothers, N = 3 parents together) at a median time of 19.0 months after DCM diagnosis (range 10.0-65.0 months; see Table 1). Compared with the normative data of same-aged children (8.0% borderline or clinical score), a significantly larger proportion of children with DCM (24.0% borderline or clinical score) showed somatic complaints in the borderline or clinical range, p < .001. In contrast, the proportion of children showing a borderline or clinical level of externalizing problems was significantly smaller in the DCM study group (5.4% clinical or borderline score) than in the general population (17.0% borderline or clinical score), p = .049.

For the other scales, the proportions of borderline and clinical problems in children with DCM and children from the general population did not significantly differ. However, trends towards significance were found for more emotionally reactive (p = .062) and depressive problems (p = .062), and less attention deficit/hyperactivity problems (p = .068).

Six- to 18-year-old children (CBCL/6-18)

The distribution of parent-reported emotional and behavioral problems in 6- to 18-year-old children with DCM and children from the general population is shown in Table 3. The CBCL/6-18 was completed for 31 children (by n = 5 fathers, n = 23 mothers, n = 3 parents together) at a median time of 39.0 months after DCM diagnosis (range 12.0-177.0 months; see Table 1). Compared with normative data of same-aged peers, significantly larger proportions of children with DCM showed problems in the borderline or clinical range on the following scales: Internalizing Problems (p = .001; 17.0% vs. 38.7%), anxious/depressed problems (p = .023; 8.0% vs. 19.4%), somatic complaints (p < .001; 8.0% vs. 29.0%), depressive problems (p < .001; 8.0% vs. 29.0%), anxiety problems (p = .023; 8.0% vs. 19.4%), and somatic problems (p < .001; 8.0% vs. 25.8%). For the other scales, the proportion of borderline and clinical problems did not significantly differ between children with DCM and children from the general population.

Table 2 Distribution of non-clinical versus borderline/clinical emotional and behavioral problems reported by parents of 1.5- to 5-year-old children (CBCL 1½-5).

CBCL 1½-5 scale	DCM patients (*n* = 37) *		General population		
	Non-clinical, *n* (%)	Borderline/clinical, *n* (%)	Non-clinical %	Borderline/clinical %	*p*-value
Broadband scales					
Internalizing Problems	29 (78.4%)	8 (21.6%)	83%	17%	.298
Externalizing Problems	35 (94.6%)	2 (5.4%)	83%	17%	**.049**
Total Problems	31 (83.8%)	6 (16.2%)	83%	17%	.500
Syndrome scales					
Anxious/Depressed	36 (97.3%)	1 (2.7%)	92%	8%	.188
Somatic Complaints	28 (75.7%)	9 (24.3%)	92%	8%	**< .001**
Attention Problems	36 (97.3%)	1 (2.7%)	92%	8%	.188
Aggressive Behavior	35 (94.6%)	2 (5.4%)	92%	8%	.390
Emotionally Reactive	31 (83.8%)	6 (16.2%)	92%	8%	.062
Withdrawn	33 (89.2%)	4 (10.8%)	92%	8%	.372
Sleep Problems	34 (91.9%)	3 (8.1%)	92%	8%	.500
DSM-oriented scales					
Depressive Problems	31 (83.8%)	6 (16.2%)	92%	8%	.062
Anxiety Problems	32 (86.5%)	5 (13.5%)	92%	8%	.175
Attention Deficit/Hyperactivity Problems	37 (100%)	0 (0%)	92%	8%	.068
Oppositional Defiant Problems	36 (97.3%)	1 (2.7%)	92%	8%	.188
Autism Spectrum Problems	34 (91.9%)	3 (8.1%)	92%	8%	.500

* Reported by fathers (*n*=9), mothers (*n*=25), or both parents together (*n*=3).

Table 3 Distribution of non-clinical versus borderline/clinical emotional and behavioral problems reported by parents of 6- to 18-year-old children (CBCL/6-18).

CBCL/6-18 scale	DCM patients (*n* = 31)[a]		General population		
	Non-clinical, *n* (%)	Borderline/clinical, *n* (%)	Non-clinical %	Borderline/clinical %	*p*-value
Broadband scales					
Internalizing Problems	19 (61.3%)	12 (38.7%)	83%	17%	**.001**
Externalizing Problems	28 (90.3%)	3 (9.7%)	83%	17%	.199
Total Problems	26 (83.8%)	5 (16.1%)	83%	17%	.500
Syndrome scales					
Anxious/Depressed	25 (80.6%)	6 (19.4%)	92%	8%	**.023**
Withdrawn/Depressed	28 (90.3%)	3 (9.7%)	92%	8%	.495
Somatic Complaints	22 (71.0%)	9 (29.0%)	92%	8%	**< .001**
Social Problems	28 (90.3%)	3 (9.7%)	92%	8%	.495
Thought Problems	26 (83.9%)	5 (16.1%)	92%	8%	.091
Attention Problems	27 (87.1%)	4 (12.9%)	92%	8%	.250
Rule Breaking Behavior	31 (100%)	0 (0%)	92%	8%	.095
Aggressive Behavior	29 (93.5%)	2 (6.5%)	92%	8%	.500
DSM-oriented scales					
Depressive Problems	22 (71.0%)	9 (29.0%)	92%	8%	**< .001**
Anxiety Problems	25 (80.6%)	6 (19.4%)	92%	8%	**.023**
Somatic Problems	23 (74.2%)	8 (25.8%)	92%	8%	**< .001**
Attention Deficit/Hyperactivity Problems	28 (90.3%)	3 (9.7%)	92%	8%	.495
Oppositional defiant problems	28 (90.3%)	3 (9.7%)	92%	8%	.495
Conduct problems	29 (93.5%)	2 (6.5%)	92%	8%	.500

[a] Reported by fathers (*n*=5), mothers (*n*=23), or both parents together (*n*=3).

Predictive value of anxiety and depressive problems on endpoint

We examined whether anxiety and depressive symptoms predicted the combined risk of death or cardiac transplantation whilst controlling for NYU PHFI. The proportional hazard assumptions were not violated. Before July 1, 2017, 11 participants (16.2%) had reached an endpoint. One had died and 10 had undergone cardiac transplantation. The results of the Cox regression analysis are presented in Table 4. Anxiety problems and depressive problems did not significantly predict death or cardiac transplantation. However, the NYU PHFI did significantly predict the risk of death or cardiac transplantation, $p < .001$. A one unit increase in the NYU PHFI resulted in a 42% higher risk of death or cardiac transplantation (hazard ratio 1.42, 95% confidence interval 1.19-1.69).

Table 4 Results of Cox regression analysis.

		95% CI*		
Variable	**HR†**	**Lower**	**Upper**	***p*-value**
Anxiety Problems (t-score)	0.98	0.89	1.09	.72
Depressive Problems (t-score)	0.98	0.88	1.08	.64
NYU PHFI‡ (per unit)	1.42	1.19	1.69	< .001

*CI = confidence interval
† HR = hazard ratio
‡ NYU PHFI = New York University Pediatric Heart Failure Index

DISCUSSION

The current study is the first to investigate emotional and behavioral problems in a substantial cohort of children with DCM. Some results are in line with our expectations. Importantly, we found that, compared with normative data of same-aged peers, larger percentages of older children (6-18 years old) with DCM showed overall internalizing problems, anxiety problems, and depressive problems. Also, we found trends towards significance suggesting that, compared with normative data of same-aged peers, larger percentages of younger children (1.5-5 years old) with DCM showed emotionally reactive problems and depressive problems. These results are in line with meta-analyses in adult heart failure populations, which demonstrate an increased risk of anxiety and depression [13, 14].

Until now, only two studies have examined emotional and behavioral problems in children with DCM. The first study was conducted by Wray and Radley-Smith [19]

who found that 50% of the children with cardiomyopathy in their study (n=19, age 3½-17 years) showed a clinical level of overall emotional and behavioral problems on the CBCL questionnaire. In our study, this percentage was markedly lower (i.e., 10.8% in younger children and 16.1% in older children). This difference may be due to the fact that all children with cardiomyopathy in Wray and Radley-Smith's study were listed for cardiac transplantation, whereas in our study this was not the case.

In the second study, Menteer and colleagues [20] compared the level of depressive symptoms in children (aged 7-21 years) with DCM (n = 15), children who had successfully undergone cardiac transplantation for heart failure (n = 23), and healthy children (n = 24). In contrast to our results, they found similar levels of depressive symptoms in all groups. That is, the level of depressive symptoms in children with DCM did not significantly differ from the level of depressive symptoms in healthy children and children who had undergone cardiac transplantation. However, it should be noted that Menteer and colleagues used small sample sizes, which limits the statistical power to detect differences between groups. Moreover, this discordance in results may be explained by the fact that we assessed depressive problems through the CBCL questionnaire whereas Menteer and colleagues used the Children's Depression Inventory (CDI)[29]. Although both instruments assess depressive symptoms, previously, moderate correlations between CDI total scores and CBCL depressive problems scores have been found [30].

Depressive and anxiety problems in children with DCM may be caused by factors directly or indirectly related to the illness. For example, in other chronic illnesses, it has been shown that the symptoms of the illness itself [31, 32] and side effects of medical treatments [33] can provoke anxiety and depressive symptoms. More indirectly, illness uncertainty (i.e., uncertainty regarding prognosis, disease course, and treatment) can increase symptoms of depression and anxiety [31, 34]. This can be explained by the cognitive coping theory [35], which states that children interpret situations based on previous knowledge and experiences. When such information is lacking, a situation may be interpreted as a threat, which consequently increases symptoms of depression and anxiety [31, 36-39]. Similarly, medical treatments such as injections may be experienced as distressing and threatening, thereby increasing children's anxiety levels [31]. Furthermore, it is known that parental overprotectiveness can promote anxiety and depressive symptoms in children with a chronic illness [31, 34, 40]. Depressive and anxiety problems may also have a biological cause. In adult [41, 42] and pediatric [43] heart failure populations, reduced brain tissue volumes have been found in brain areas which regulate mood.

Future research is needed to draw definite conclusions as to biological causes of mood problems in DCM.

Besides increased anxiety and depressive problems, we demonstrated that, compared with normative data, a larger percentage of young and older children with DCM showed a borderline or clinical level of somatic problems. This is not surprising considering all children had heart failure problems secondary to DCM. Furthermore, previous studies have reported reduced levels of physical health related quality of life in this population [15].

Other results of the current study were unexpected or contrary to our hypotheses. Firstly, we found that, compared with normative data, a smaller percentage of young children with DCM showed a borderline or clinical level of externalizing problems. In line with this result, we found a trend towards significance suggesting that, compared with normative data, a smaller percentage of young children with DCM showed attention deficit/hyperactivity problems. This might be explained by increased levels of fatigue reported in DCM [5], which may contribute to children showing less hyperactive behavior.

Secondly, contrary to our hypothesis, we found that anxiety and depressive problems in children with DCM did not predict the risk of death and cardiac transplantation whilst controlling for heart failure severity. However, in line with the results of a previous DCM study, heart failure severity (NYU PHFI) did predict the risk of death and cardiac transplantation [15]. In contrast with our findings, in adult heart failure populations, a multitude of studies have shown that depressive problems predict mortality and other adverse clinical outcomes [e.g., 13, 21, 44, 45-48]. Furthermore, increasing evidence shows that anxiety problems predict mortality in adult heart failure [22]. An explanation for our different findings is that, in adults, depressive and anxiety problems can lead to poorer self-care [49]. In children, however, parents may compensate for children's poorer self-care behaviors which subsequently diminishes the impact of depressive and anxiety problems on their physical health. Also, it should be noted that statistical power to detect associations was limited.

This study has several strengths. Studies exclusively examining pediatric cardiomyopathy patients are scarce [12]. As stated, the current study is the first to examine emotional and behavioral problems in a relatively large cohort of children with DCM. We recruited children with DCM through seven tertiary centers for

pediatric cardiology. Also, we investigated problems in a broad age range (1.5 to 18 years), using an internationally well-validated questionnaire (CBCL) to assess a wide range of emotional and behavioral problems. The multicenter recruitment and the inclusion of a broad age range improve the generalizability of our results in the pediatric DCM population. Moreover, we examined the predictive value of depressive and anxiety problems on mortality and cardiac transplantation whilst controlling for heart failure severity, which is a known predictor of adverse outcomes. Furthermore, results from our study population were compared to representative normative data matched on age and gender.

The results of this study must also be interpreted in light of a few limitations. Firstly, although the study sample is relatively large considering the prevalence of DCM, the number of events in the study was 11, which limits the statistical power of the prediction analyses. Secondly, we only used proxy-reports completed by parents because most participating children were too young to complete the self-report version of the CBCL [50]. Of the children who were old enough to complete the self-report version of the CBCL an insufficient number to analyze completed the questionnaire. The use of proxy-reports has been frequently debated. Studies have found that parent proxy-reports of quality of life in pediatric cardiac populations may differ from child self-reports [51, 52]. In another pediatric cardiac population, Patel and colleagues [53] found that parent-child agreement was stronger for more readily observable variables such as physical functioning and externalizing behavior and lower for variables which tend to be less visible, such as anxiety, emotional functioning, and internalizing behavior. In contrast, in a pediatric cardiac population, Marino and colleagues [54] found that parent-proxy reports and child self-reports on quality of life did not differ. Moreover, Wilmot and colleagues [16] reported moderate parent-child agreement on quality of life of children with cardiomyopathy. Considering the scarcity of research into emotional and behavioral problems in children with DCM, further research is needed using well-attuned self-reports as well. Thirdly, we combined both father and mother reports in our analyses. Although this may induce bias [55], it should be noted that the majority of questionnaires were completed by mothers and previous research has found moderately high inter-parent agreement on the CBCL [56]. Fourthly, considering the relatively long period of time between DCM diagnosis and participation in the current study (see Table 1), it should be noted that the current cohort represents children with chronic heart failure. Children who reached an endpoint or recovered shortly after diagnosis are likely underrepresented.

In conclusion, this first study specifically examining emotional and behavioral problems of children with DCM showed, compared with normative data, significantly more borderline or clinical levels of anxiety, depressive problems, and somatic problems in 6-18-year-olds and significantly more borderline or clinical somatic problems and less externalizing problems in 1.5-5-year-olds. These findings demonstrate the importance of including routine screening for internalizing problems to the clinical management of children with DCM [10] and of providing psychosocial support attuned to the needs of these children. Considering the previously mentioned influence of parental behavior on anxiety and depressive symptoms in pediatric chronic illness, such psychosocial support should not only focus on the children themselves but also include their parents. Future research should focus on evidence-based psychosocial programs to treat and prevent internalizing problems in pediatric cardiomyopathy. As the available literature on emotional and behavioral wellbeing in pediatric cardiomyopathy is limited, many aspects remain to be studied. Considering previous adult studies and our findings, future research should focus on anxiety and depression in pediatric DCM. Moreover, as the results of our study show that emotional and behavioral problems in DCM seem to differ per age group, it would be useful to examine this in more age groups. Furthermore, a previous study [15], found that HRQoL in children with DCM was more impaired at diagnosis than more than 1 year after diagnosis. Whether this is also the case for emotional and behavioral problems remains to be studied. Also, since little is known about the psychosocial wellbeing of children with cardiomyopathy, future qualitative studies would be valuable.

DECLARATION OF CONFLICTING INTERESTS

The Authors declare that there is no conflict of interest.

FUNDING

This work was supported by the Netherlands Heart Foundation/"Stichting Hartedroom" [grant number 2013T087].

REFERENCES

1. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med. 2003; 348: 1647-55.
2. Nugent AW, Daubeney PE, Chondros P, Carlin JB, Cheung M, Wilkinson LC, et al. The epidemiology of childhood cardiomyopathy in Australia. N Engl J Med. 2003; 348: 1639-46.
3. Jefferies JL, Towbin JA. Dilated cardiomyopathy. Lancet. 2010; 375: 752-62.
4. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA. 2006; 296: 1867-76.
5. Weintraub RG, Semsarian C, Macdonald P. Dilated cardiomyopathy. Lancet 2017; 390: 400-14.
6. Everitt MD, Sleeper LA, Lu M, Canter CE, Pahl E, Wilkinson JD, et al. Recovery of echocardiographic function in children with idiopathic dilated cardiomyopathy: results from the pediatric cardiomyopathy registry. J Am Coll Cardiol. 2014; 63: 1405-13.
7. Alexander PM, Daubeney PE, Nugent AW, Lee KJ, Turner C, Colan SD, et al. Long-term outcomes of dilated cardiomyopathy diagnosed during childhood: results from a national population-based study of childhood cardiomyopathy. Circulation. 2013; 128: 2039-46.
8. den Boer SL, Lennie van Osch-Gevers M, van Ingen G, du Marchie Sarvaas GJ, van Iperen GG, Tanke RB, et al. Management of children with dilated cardiomyopathy in The Netherlands: Implications of a low early transplantation rate. J Heart Lung Transplant. 2015; 34: 963-9.
9. Boucek MM, Waltz DA, Edwards LB, Taylor DO, Keck BM, Trulock EP, et al. Registry of the International Society for Heart and Lung Transplantation: ninth official pediatric heart transplantation report--2006. J Heart Lung Transplant. 2006; 25: 893-903.
10. Kirk R, Dipchand AI, Rosenthal DN, Addonizio L, Burch M, Chrisant M, et al. The International Society for Heart and Lung Transplantation Guidelines for the management of pediatric heart failure: Executive summary. [Corrected]. J Heart Lung Transplant. 2014; 33: 888-909.
11. Rossano JW, Cherikh WS, Chambers DC, Goldfarb S, Khush K, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Twentieth Pediatric Heart Transplantation Report-2017; Focus Theme: Allograft ischemic time. J Heart Lung Transplant. 2017; 36: 1060-9.
12. Glotzbach K, May L, Wray J. Health related quality of life and functional outcomes in pediatric cardiomyopathy. Progr Pediatr Cardiol. 2018; 48: 26-35.
13. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol. 2006; 48: 1527-37.

14. Fan H, Yu W, Zhang Q, Cao H, Li J, Wang J, et al. Depression after heart failure and risk of cardiovascular and all-cause mortality: a meta-analysis. Prev Med. 2014; 63: 36-42.

15. den Boer SL, Baart SJ, van der Meulen MH, van Iperen GG, Backx AP, Ten Harkel AD, et al. Parent reports of health-related quality of life and heart failure severity score independently predict outcome in children with dilated cardiomyopathy. Cardiol Young. 2017; 27: 1194-202.

16. Wilmot I, Cephus CE, Cassedy A, Kudel I, Marino BS, Jefferies JL. Health-related quality of life in children with heart failure as perceived by children and parents. Cardiol Young. 2016; 26: 885-93.

17. Sleeper LA, Towbin JA, Colan SD, Hsu D, Orav EJ, Lemler MS, et al. Health-Related Quality of Life and Functional Status Are Associated with Cardiac Status and Clinical Outcome in Children with Cardiomyopathy. J Pediatr. 2016; 170: 173-80.

18. Hollander SA, Callus E. Cognitive and psycholologic considerations in pediatric heart failure. J Card Fail. 2014; 20: 782-5.

19. Wray J, Radley-Smith R. Cognitive and behavioral functioning of children listed for heart and/or lung transplantation. Am J Transplant. 2010; 10: 2527-35.

20. Menteer J, Beas VN, Chang JC, Reed K, Gold JI. Mood and health-related quality of life among pediatric patients with heart failure. Pediatr Cardiol. 2013; 34: 431-7.

21. Celano CM, Villegas AC, Albanese AM, Gaggin HK, Huffman JC Depression and Anxiety in Heart Failure: A Review. Harv Rev Psychiatry. 2018; 26: 175-84.

22. Vongmany J, Hickman LD, Lewis J, Newton PJ, Phillips JL. Anxiety in chronic heart failure and the risk of increased hospitalisations and mortality: A systematic review. Eur J Cardiovasc Nurs. 2016; 15: 478-85.

23. Rickham PP. Human Experimentation. Code of Ethics of the World Medical Association. Declaration of Helsinki. Br Med J. 1964; 2: 177.

24. Achenbach TM, Becker A, Dopfner M, Heiervang E, Roessner V, Steinhausen HC, et al. Multicultural assessment of child and adolescent psychopathology with ASEBA and SDQ instruments: research findings, applications, and future directions. J Child Psychol Psychiatry. 2008; 49: 251-75.

25. International Standard Classification of Occupations: ISCO-08. Geneva: International Labour Organization; 2012.

26. Connolly D, Rutkowski M, Auslender M, Artman M. The New York University Pediatric Heart Failure Index: a new method of quantifying chronic heart failure severity in children. J Pediatr. 2001; 138: 644-8.

27. Achenbach TM, Rescorla LA. Manual for the ASEBA school-age forms & profiles. Burlington, Vermont: University of Vermont, Research Center for Children, Youth, & Families; 2001.

28. IBM Corp. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp; 2016.

29. Kovacs M. Rating scales to assess depression in school-aged children. Acta Paedopsychiatr. 1981; 46: 305-15.

30. Nakamura BJ, Ebesutani C, Bernstein A, Chorpita BF. A psychometric analysis of the Child Behavior Checklist DSM-Oriented Scales. J Psychopathol Behav Assess. 2009; 31.

31. Pinquart M, Shen Y. Anxiety in children and adolescents with chronic physical illnesses: a meta-analysis. Acta Paediatr. 2011; 100: 1069-76.

32. Hommel KA, Chaney JM, Wagner JL, White MM, Hoff AL, Mullins LL. Anxiety and depression in older adolescents with long-standing asthma: The role of illness uncertainty. Children's Health Care. 2003; 32: 51-63.

33. Miller JM, Kustra RP, Vuong A, Hammer AE, Messenheimer JA. Depressive symptoms in epilepsy: prevalence, impact, aetiology, biological correlates and effect of treatment with antiepileptic drugs. Drugs. 2008; 68: 1493-509.

34. Pinquart M, Shen Y. Depressive symptoms in children and adolescents with chronic physical illness: an updated meta-analysis. J Pediatr Psychol. 2011; 36: 375-84.

35. Mishel MH. The measurement of uncertainty in illness. Nurs Res. 1981; 30: 258-63.

36. Steele RG, Aylward BS, Jensen CD, Wu YP. Parent-and youth-reported illness uncertainty: Associations with distress and psychosocial functioning among recipients of liver and kidney transplantations. Children's Health Care. 2009; 38: 185-99.

37. Fortier MA, Batista ML, Wahi A, Kain A, Strom S, Sender LS. Illness uncertainty and quality of life in children with cancer. J Pediatr Hematol Oncol. 2013; 35: 366-70.

38. Stewart JL, Mishel MH. Uncertainty in childhood illness: a synthesis of the parent and child literature. Sch Inq Nurs Pract. 2000; 14: 299-319.

39. Pao M, Bosk A. Anxiety in medically ill children/adolescents. Depress Anxiety. 2011; 28: 40-9.

40. Pinquart M. Do the parent-child relationship and parenting behaviors differ between families with a child with and without chronic illness? A meta-analysis. J Pediatr Psychol. 2013; 38: 708-21.

41. Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM. Regional brain gray matter loss in heart failure. J Appl Physiol. 2003; 95: 677-84.

42. Woo MA, Macey PM, Keens PT, Kumar R, Fonarow GC, Hamilton MA, et al. Functional abnormalities in brain areas that mediate autonomic nervous system control in advanced heart failure. J Card Fail. 2005; 11: 437-46.

43. Menteer J, Macey PM, Woo MA, Panigrahy A, Harper RM. Central nervous system changes in pediatric heart failure: a volumetric study. Pediatr Cardiol. 2010; 31: 969-76.

44. Rumsfeld JS, Havranek E, Masoudi FA, Peterson ED, Jones P, Tooley JF, et al. Depressive symptoms are the strongest predictors of short-term declines in health status in patients with heart failure. J Am Coll Cardiol. 2003; 42: 1811-7.

45. Junger J, Schellberg D, Muller-Tasch T, Raupp G, Zugck C, Haunstetter A, et al. Depression increasingly predicts mortality in the course of congestive heart failure. Eur J Heart Fail. 2005; 7: 261-7.

46. Sherwood A, Blumenthal JA, Hinderliter AL, Koch GG, Adams KF, Jr., Dupree CS, et al. Worsening depressive symptoms are associated with adverse clinical outcomes in patients with heart failure. J Am Coll Cardiol. 2011; 57: 418-23.

47. Sokoreli I, Pauws SC, Steyerberg EW, de Vries GJ, Riistama JM, Tesanovic A, et al. Prognostic value of psychosocial factors for first and recurrent hospitalizations and mortality in heart failure patients: insights from the OPERA-HF study. Eur J Heart Fail. 2018; 20: 689-96.

48. Angermann CE, Ertl G. Depression, Anxiety, and Cognitive Impairment: Comorbid Mental Health Disorders in Heart Failure. Curr Heart Fail Rep. 2018; 15: 398-410.

49. Luyster FS, Hughes JW, Gunstad J. Depression and anxiety symptoms are associated with reduced dietary adherence in heart failure patients treated with an implantable cardioverter defibrillator. J Cardiovasc Nurs. 2009; 24: 10-7.

50. Achenbach TM. Manual for the Youth Self-Report and 1991 Profile. Burlington: University of Vermont Department of Psychiatry; 1991.

51. Berkes A, Varni JW, Pataki I, Kardos L, Kemeny C, Mogyorosy G. Measuring health-related quality of life in Hungarian children attending a cardiology clinic with the Pediatric Quality of Life Inventory. Eur J Pediatr. 2010; 169: 333-47.

52. Uzark K, Jones K, Slusher J, Limbers CA, Burwinkle TM, Varni JW. Quality of life in children with heart disease as perceived by children and parents. Pediatrics. 2008; 121: 1060-7.

53. Patel BJ, Lai L, Goldfield G, Sananes R, Longmuir PE. Psychosocial health and quality of life among children with cardiac diagnoses: agreement and discrepancies between parent and child reports. Cardiol Young. 2017; 27: 713-21.

54. Marino BS, Shera D, Wernovsky G, Tomlinson RS, Aguirre A, Gallagher M, et al. The development of the pediatric cardiac quality of life inventory: a quality of life measure for children and adolescents with heart disease. Qual Life Res. 2008; 17: 613-26.

55. Janse AJ, Sinnema G, Uiterwaal CSPM, Kimpen JLL, Gemke RJBJ. Quality of life in chronic illness: Children, parents and paediatricians have different, but stable perceptions. Acta Paediatrica. 2008; 97.

56. Schroeder JF, Hood MM, Hughes HM. Inter-parent agreement on the syndrome scales of the Child Behavior Checklist (CBCL): Correspondence and discrepancies. J Child Fam Stud. 2010; 19.

6

CHAPTER 6

EMDR for children with medically related subthreshold PTSD: short-term effects on PTSD, blood-injection-injury phobia, depression and sleep

Maya G. Meentken, Malindi van der Mheen, Ingrid M. van Beynum, Elisabeth W. C. Aendekerk, Jeroen S. Legerstee, Jan van der Ende, Riwka del Canho, Ramón J. L. Lindauer, Manon H.J. Hillegers, Henriette A. Moll, Wim A. Helbing, Elisabeth M. W. J. Utens

European Journal of Psychotraumatology, 2020, 11 (1)

ABSTRACT

Background. Pediatric illness, injury and medical procedures are potentially traumatic experiences with a range of possible negative psychosocial consequences. To prevent psychosocial impairment and improve medical adherence, evidence-based psychotherapy should be offered if indicated. Eye movement desensitization and reprocessing (EMDR) has been found to reduce symptoms of posttraumatic stress disorder (PTSD) in adults. The evidence for the use with children is promising. Furthermore, recent studies indicate its effectiveness for the treatment of other psychological symptomatology. However, the effectiveness of EMDR in children with subthreshold PTSD after medically related trauma has not yet been investigated.

Objective. Investigating the short-term effectiveness of EMDR on posttraumatic stress, anxiety, depression and sleep problems in children with subthreshold PTSD after hospitalization through a randomized controlled trial (RCT).

Method. Following baseline screening of 399 children from various Dutch hospitals, 74 children (4-15 years old) with medically related subthreshold PTSD were randomized to EMDR (n=37) or care-as-usual (CAU; n=37). Follow-up assessment took place after M=9.7 weeks. Generalized Estimating Equation (GEE) analyses were performed to examine the effectiveness of EMDR compared to CAU.

Results. Children in both groups improved significantly over time on all outcomes. However, the EMDR group improved significantly more as to child-reported symptoms of blood-injection-injury (BII) phobia and depression, and child-, and parent-reported sleep problems of the child. There was no superior effect of EMDR compared to CAU on subthreshold PTSD symptom reduction.

Conclusions. EMDR did not perform better than CAU in reducing PTSD symptoms in a pediatric sample of children with subthreshold PTSD after hospitalization. However, the study results indicate that EMDR might be superior in reducing symptoms of blood-injection-injury phobia, depression and sleep problems.

INTRODUCTION

A growing number of studies have confirmed posttraumatic stress reactions and other psychopathological symptoms in children and adolescents after hospitalization and medical procedures [1, 2]. Although many children are resilient and show a reduction in symptoms in the weeks after the medical event, some experience long-term impairing symptomatology or even develop a mental disorder. Common symptoms after medical events are posttraumatic stress, anxiety (especially blood-injection-injury phobia), mood and sleep problems [2-5]. Prevalence rates of posttraumatic stress disorder (PTSD) in children after chronic illness (e.g., heart disease) or acute injury (e.g., after traffic accidents) vary from 12 to 31% [6, 7]. PTSD is a serious mental disorder which is associated with substantial impairment in cognitive, academic, social and emotional functioning [8-11]. Similar impairment is seen in children with subthreshold PTSD (i.e. not meeting all criteria for a full diagnostic PTSD), which is even more common than full diagnostic PTSD, namely 25-38% [1, 2, 12, 13]. These findings underscore the clinical significance of subthreshold PTSD and suggest a need for appropriate treatment options. However, subthreshold PTSD is often overlooked and stays untreated which can lead to worsening of the symptoms and full diagnostic PTSD [14]. While treatment possibilities for full diagnostic PTSD are widely studied, evaluations of treatment options for subthreshold PTSD are very scarce [15, 16].

Eye movement desensitization and reprocessing (EMDR) is one of the most studied evidence-based psychotherapies for PTSD treatment in adults [17-19]. Like many psychotherapies, EMDR was developed for adults and was later adapted for children. Consequently, scientific studies into the effectiveness of EMDR for children are underrepresented [20, 21]. Two meta-analyses and one review including only a few studies show promising results regarding EMDR for children [22-24]. Interestingly, a recent meta-analysis comparing the effectiveness of EMDR and cognitive behavioral therapy (CBT) showed that children with subthreshold PTSD exhibited significantly greater reductions in PTSD symptoms following treatment than those who were reported to have full diagnostic PTSD [25]. However, the effectiveness of EMDR for children has not yet been investigated focusing solely on children with subthreshold PTSD.

EMDR has originally been developed as PTSD treatment, but it has also been shown to be useful for the treatment of other mental health issues [26]. Evidence suggests that EMDR reduces symptoms of anxiety and depression in children [24, 27-29] and

sleep problems in adults [30]. However, these EMDR treatment outcomes have not yet been studied in pediatric medical settings.

The use of EMDR in medical settings was recently recommended by the developer of EMDR herself [31]. However, studies into the effectiveness of EMDR in a pediatric medical setting are scarce. Kemp and colleagues [32] found significant PTSD symptom reduction after four EMDR sessions in children (6-12 years) who were injured in motor vehicle accidents and initially met two or more PTSD criteria. However, this study had a very small sample size (controls n=14, EMDR n=13). Another small study with children who experienced a road traffic accident (n=11) found significant reductions of PTSD, general anxiety, and depression after an average of 2.4 EMDR sessions [33]. However, this study did not use a control group. A very small quasi-experimental study in Iranian children who survived serious traffic accidents also claims to show positive results of EMDR, but no firm conclusions can be drawn from the article due to methodological reasons [34]. Furthermore, a study in children who had experienced different kinds of traumas, including a small subsample of children with medically related trauma (23% accidents, 7% serious illness), also found promising results for EMDR in reducing PTSD symptoms [35]. Again, the sample size was small (CBT n=23, EMDR n=25).

Overviewing this rather unexplored field, systematic research in larger samples remains urgently needed. Our study represents the first randomized controlled trial that specifically aims to investigate the effectiveness of EMDR in reducing medically related subthreshold PTSD after hospitalization for pediatric illness or injury. Secondary aims were to test the effectiveness of EMDR in reducing children's anxiety (especially blood-injection-injury phobia), depression and sleep problems.

METHODS

Design

This randomized controlled trial (RCT) represents a single-center study. All therapy sessions took place in the Erasmus MC - Sophia children's hospital in Rotterdam, the Netherlands. Participants were recruited via the Sophia children's hospital (divisions of pediatrics and pediatric cardiology), the pediatrics division of the Maasstad hospital in Rotterdam, the pediatric cardiology division of the Radboud UMC Nijmegen, and nationally through the Dutch Association for patients with a congenital heart defect, and the Dutch non-profit organization Heartchild

Foundation (Stichting Hartekind). A detailed article about the study protocol has been published previously [36]. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center in the Netherlands, registered in the Dutch Trial Register (NTR5801), and performed conform the Declaration of Helsinki [37].

Participants

The target group was 4-15-year-old children with medically related subthreshold PTSD after >1 hospitalization(s) of at least one night. The presence of subthreshold PTSD was first investigated with the Children's Responses to Trauma Inventory (CRTI) [38]. Subthreshold PTSD was defined as either (1) fulfilling at least two of the three DSM-IV PTSD symptom criteria (re-experience, avoidance or hyperarousal) and/or (2) having an above average score (>60th percentile) on the CRTI; without a full diagnostic PTSD score on a semi-structured interview afterwards. The last hospitalization or additional medical procedure(s) should have occurred at least 4 weeks and at most 5 years ago. The inclusion period was from July 2016 until May 2018.

The screening for subthreshold PTSD took place during a baseline assessment (T1). For this assessment, we included children who had been hospitalized 1) after consultation at an emergency department due to acute injury or illness, or 2) at a pediatric cardiology department due to a congenital or acquired heart defect. Both groups encompassed children who experienced single (type I trauma) or multiple (type II trauma) medical events. In this study, we defined type I trauma as a first hospitalization of previously healthy children. Type II trauma was defined as >2 hospitalizations or an additional medical procedure (e.g. surgery) next to an one-time hospitalization.

Exclusion criteria were: (1) intellectual disability (IQ<70); (2) parental inability to read or write Dutch; (3) diagnosis of a chronic illness for the emergency department subgroup; (4) previous successful treatment for medically related PTSD; and (5) current psychological treatment.

Procedure

After informed consent was obtained, 420 participants were asked to fill out questionnaires to screen for PTSD symptoms (primary outcome) and other related psychosocial symptoms (secondary outcomes) during a baseline assessment [39]. Subsequently, children (aged 8-15 years) with baseline scores indicating at

least subthreshold levels of PTSD were invited for a semi-structured interview (Clinician-Administered PTSD Scale for Children and Adolescents, CAPS-CA) [40]. For children aged 4-7 years with at least subthreshold levels of PTSD, one parent was interviewed using the PTSD module of the Diagnostic Infant and Preschool Assessment (DIPA) [41]. Since our study focused on children with subthreshold PTSD, children with a full diagnostic PTSD score on the interview were excluded and referred for treatment. Seventy-four children with subthreshold PTSD were randomized on a 1:1 ratio into the EMDR (n=37) or care-as-usual group (CAU; n=37). Randomization was stratified by trauma type (i.e. type I vs. type II trauma) and age (i.e. 4-11 vs. 12-15) using blocks, and performed by an independent researcher using opaque envelopes. Questionnaires were filled out at baseline (T1) and during a follow-up assessment M= 9.7 (SD=2.5) weeks after the first EMDR session (T2). Of the 74 randomized children, three (EMDR n=2; CAU n=1) were erroneously randomized due to misinterpretation of their score (two children scored only one point below the cut-off). Within the EMDR group, four children did not start with EMDR at all after randomization. See figure 1 for an overview.

Measures

Children >6 years of age were asked to fill out questionnaires. Parent-report was asked for children of all included ages. Participants were asked to fill out the questionnaires with regard to a medical event. All questionnaires have adequate psychometric properties.

Primary outcome

PTSD symptoms were measured using the Dutch version of the CRTI [38]. The CRTI contains 24 PTSD items which can be divided into three subscales related to the DSM-IV-TR symptom clusters of PTSD (intrusion, avoidance, and hyperarousal). The total PTSD score can range from 17 to 85, with a higher score indicating more problems. The scores on the subscales intrusion and hyperarousal can range from 5-25 and on avoidance from 7-35.

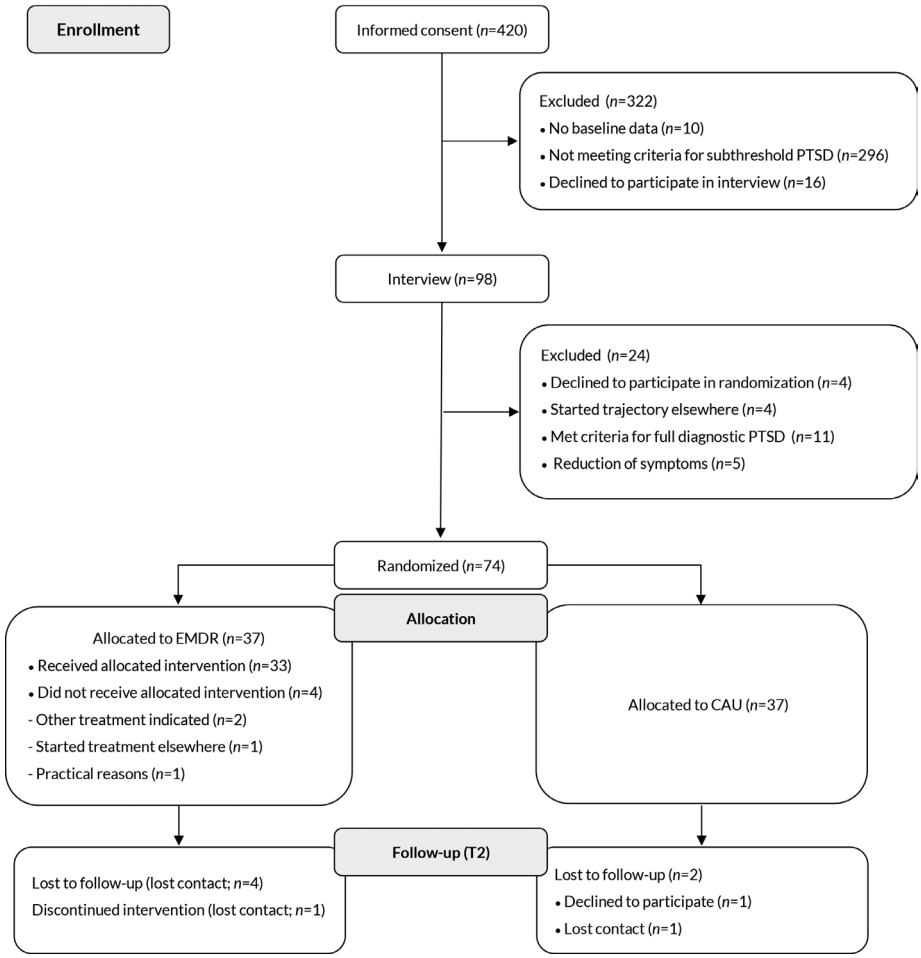
Secondary outcomes

Symptoms of depression were measured through the total score of the Dutch Children's Depression Inventory 2 (CDI-2) [42]. The parent version contains 17 items with a 4-point Likert scale and the child version contains 28 items with a 3-point Likert scale. Scores can range from 0 to 51 (parent-version) or 56 (child-version). A higher score indicates more problems.

Symptoms of the blood-injection-injury (BII) phobia and anxiety in general were measured through the BII subscale (7 items) and the total score (69 items) of the Dutch Screen for Child Anxiety Related Emotional Disorders (SCARED-NL) [43]. Responses are scored on a 3-point Likert scale (0-2) with a maximum score of 14 (BII subscale) and 138 (total score). A higher score indicates more problems.

Sleep problems were measured using the total score of the Dutch Sleep Self Report (SSR, 23 items) [44] and the Dutch parallel parent version called Child Sleep Habits Questionnaire (CSHQ, 35 items) [45]. Responses are rated on a 3-point Likert scale (1-3) with maximum total scores of 69 (SSR) and 99 (CSHQ). Again, a higher score indicates more sleep problems.

Figure 1 Participation flow chart.



Social validity questions were added to investigate parents' and children's subjective evaluation of the EMDR treatment. Three aspects of social validity (satisfaction with EMDR, usefulness of EMDR and recommendation of EMDR) were assessed in the EMDR group at T2. A 10-point Likert scale (0-10) was used with a higher score indicating more satisfaction, perceived usefulness and willingness to recommend EMDR.

Intervention

EMDR is based on the assumption that traumatic memories are stored inadequately. During therapy, the child is asked to think about a currently disturbing memory while simultaneously focusing on a bilateral stimulation (i.e. eye movements). This initiates processing of the memory. The working mechanism of EMDR is still unclear. The hypothesis with most support is that engaging in two simultaneous tasks (i.e. eye movements and thinking about a disturbing memory) draws on the limited capacity of the working memory and therefore decreases the vividness of the image [46].

Children in the EMDR group received *M*=3.5 (*SD*=1.9) EMDR sessions (intake included) of approximately 50 minutes. Parents were allowed to be present during the sessions when the child agreed on this with the therapist. EMDR therapy was provided by five licensed and experienced clinical psychologists following the standard Dutch EMDR protocol for children and adolescents [47] or the adapted version for young children [48, 49]. EMDR treatment was completed when (1) Subjective Units of Distress (SUDs) of all selected memories regarding the medical trauma were zero and/or (2) positive cognitions were established (rated by the child) and/or (3) child, parents and therapist agreed that PTSD symptoms had sufficiently decreased. Children in the CAU group only received standard medical care.

Treatment integrity

All five EMDR-therapists participated in regular supervision sessions provided by a EMDR Europe consultant (licensed supervisor). All EMDR sessions were videotaped. If no consent for videotaping was obtained, the therapists provided detailed written records. All sessions of 10 randomly chosen children (27%) were rated on protocol adherence by a trained research psychologist and two trained Master students in psychology, supervised by the aforementioned research psychologist. Rating was done with an EMDR-specific treatment integrity checklist with a total score ranging from 0-16. There was good agreement between all three independent

raters: all total scores given ranged between 13-16. Treatment integrity was high with 95%.

Statistical analyses

We conducted t-tests and χ2-tests to test differences between the EMDR and CAU group baseline characteristics. Correlations between child and parent report were analyzed using Pearson's *r* and differences were tested using paired sample t-test. To test for differences in outcome scores between both groups in the total sample, Generalized Estimating Equations (GEE) with an unstructured correlation matrix were performed following the intention-to-treat principle. We conducted a GEE analysis for each outcome separately. In each analysis, we first added time (T1 vs. T2) and group (EMDR vs. CAU) as factors. Interactions between time and group were tested for significance with Wald χ^2 tests. Second, if the interaction was significant, we ran the GEE analyses again adding age, gender and whether the child had experienced >1 other non-medical stressful life events as covariates. Third, for all significant interactions, we also added trauma type, hospital department, and time since last medical event as covariates and, for explorative analyses, their interaction with time and group.

In addition, we ran the analyses of the first step again 1) following the per-protocol principle and 2) without the three erroneously randomized children. Effect sizes were measured with Cohen's *d* by dividing the difference between the estimated means of both groups at T2 by the pooled standard deviation at T1 [50]. SPSS version 24.0 was used for all statistical analyses.

RESULTS

Baseline characteristics

At baseline, no differences were found between the EMDR and CAU group with regard to baseline demographics. See Table 1 for more information. However, the EMDR group had a significantly higher mean score at baseline on the child-reported total sleep problem score than the CAU group [$t(65) = -2.3$, $p<.05$].

Parent-child agreement

PTSD symptoms. The correlation between child and parent report on the primary outcome (CRTI) was moderate ($r=.31$) at T1 and high ($r=.56$) at T2. Differences between child and parent report at the two time points were not significant.

Symptoms of depression. The correlation between parent and child report on depression was high at T1 (r=.58) and T2 (r=.76). Differences between child and parent report could not be tested due to incomparable questionnaires.

Symptoms of BII phobia and anxiety in general. Parent and child report for BII phobia was high at T1 (r=.71) and T2 (r=.75). There were significant differences in the T1 scores for parent report (M=5.06, SD=3.16) and child report (M=5.76, SD=3.21); $t(66)$=-2.35, p=.02. The correlation between parent and child report on the SCARED-NL total score was also high at T1 (r=.53) and T2 (r=.75). There were no significant differences between child and parent report.

Sleep problems. The correlation between child and parent report on sleep problems were high at T1 (r=.53) and T2 (r=.79). To test for differences between child and parent reported sleep problems, CSHQ total scores were divided by 35 (number of CSHQ items) and then multiplied by 23 (number of SSR items). At both assessment points, children (M_{T1}= 37.09, SD_{T1}=5.97; M_{T2}=34.18, SD_{T2}=6.36) reported significantly more sleep problems than parents (M_{T1}= 32.70, SD_{T1}=5.47; M_{T2}=30.23, SD_{T2}=5.50); $t_{T1}(66)$=-6.47, p=.00 and $t_{T2}(56)$=-7.56, p=.00.

Primary outcome

Outcomes of the EMDR and CAU group are shown in Table 2. Children in both groups showed a similar reduction in PTSD symptoms from baseline to follow-up. EMDR was not significantly superior compared to CAU in reducing child-reported (b=-0.5, p=.853) and parent-reported (b=-3.5, p=.275) PTSD symptoms of the child. The same was true for all three PTSD subscales.

Secondary outcomes

From baseline to follow-up, child-reported symptoms of blood-injection-injury phobia decreased significantly more in the EMDR group than in the CAU group (b=-1.5, p=.034). This effect remained significant in a secondary GEE analysis controlling for age, gender and other stressful life events (b=-1.5, p=.034, Cohen's d=-.46). In contrast, parent-reported BII phobia symptom reduction in the child did not differ significantly between the EMDR group and the CAU group (b=-0.5, p=.364).

As to child-reported anxiety symptoms, EMDR was not superior in reducing child-reported total anxiety symptoms compared to CAU (b=-6.8, p=.101). The same was true for parent-reported total child anxiety symptoms (b=-3.8, p=.288).

Child-reported symptoms of depression declined significantly more in the EMDR group than in the CAU group (*b*=-2.5, *p*=.037). This effect remained significant after controlling for age, gender and other stressful life events (*b*=-2.5, *p*=.037, Cohen's *d*=-.40). As to parent-reported symptoms of depression of the child, a trend towards significance in favor of the EMDR group was found (*b*=-2.6, *p*=.05).

With regard to child-reported sleep problems we found a significant larger reduction from baseline to follow-up for the EMDR group compared with the CAU group (*b*=-3.6, *p*=.003). This effect remained significant after controlling for age, gender and other stressful life events (*b*=-3.6, *p*=.003, Cohen's *d*=-.63). Children's sleep problems reported by the parents also reduced significantly more in the EMDR group than the CAU group (*b*=-2.8, *p*=.032). However, this effect was not significant anymore after controlling for age, gender and other stressful life events (*b*=-2.6, *p*=.059, Cohen's *d*=-.31).

Explorative analyses

No significant differences in treatment effect were found for trauma type and hospital department. However, the effect of EMDR in reducing child-reported symptoms of depression and sleep problems were larger the longer ago the last medical event happened.

Additional analyses

Per-protocol analyses revealed some minor deviations regarding the secondary outcomes compared to intention-to-treat analyses. In addition to the findings that EMDR was superior to CAU in treating BII phobia (child-report), depression (child-report) and sleep problems (child-report and parent-report), per-protocol analyses showed that EMDR was also superior in treating parent-reported symptoms of depression of the child and child-reported total anxiety score.

Furthermore, we did another analysis without the children who were erroneously randomized. In contrast to the previous analyses, improvements between baseline and follow-up regarding child-reported depressive symptoms and parent-reported sleep problems of the child were not significantly larger for the EMDR group anymore. However, the superior effects of EMDR on child-reported BII phobia symptoms and child-reported sleep problems remained significant.

Table 1 Baseline demographics.

Variable	N	Total	EMDR group (*n*=37)	CAU group (n=37)	p-value
Child					
Age in years, *M* ± *SD*	74	9.6 ± 2.9	9.8 ± 2.7	9.4 ± 3.1	.604
Gender, *n* (%)	74				.806
Girls		25 (33.8)	12 (32.4)	13 (35.1)	
Boys		49 (66.2)	25 (67.6)	24 (64.9)	
Ethnicity, *n* (%)	72				.202
Dutch		59 (81.9)	32 (88.9)	27 (75.0)	
Other Western		4 (5.6)	2 (5.6)	2 (5.6)	
Non-Western		9 (12.5)	2 (5.6)	7 (19.4)	
Other stressful life events, *n* (%)	67				.864
Yes		55 (82.1)	29 (82.9)	26 (81.3)	
No		12 (17.9)	6 (17.1)	6 (18.8)	
Parental					
Education, *n* (%)	74				.836
High		41 (55.4)	21 (56.8)	20 (54.1)	
Medium		30 (40.5)	15 (40.5)	15 (40.5)	
Low		3 (4.1)	1 (2.7)	2 (5.4)	

Table 1 Continued

Variable	N	Total	EMDR group (*n*=37)	CAU group (n=37)	p-value
Medical					
Department, *n* (%)	74				.816
Cardiology		39 (52.7)	19 (51.4)	20 (54.1)	
Emergency unit		35 (47.3)	18 (48.6)	17 (45.9)	
Trauma type, *n* (%)	74				.572
I		16 (21.6)	9 (24.3)	7 (18.9)	
II		58 (78.4)	28 (75.7)	30 (81.1)	
No. of hospitalizations, *M* ± *SD*	71	4.01 ± 4.00	4.5 ± 4.4	3.6 ± 3.5	.331
Length of hospitalization(s) in days, *M* ± *SD*	59	28.14 ± 47.23	31.7 ± 54.9	24.2 ± 37.6	.545
Time since last medical event in years, *M* ± *SD*	71	1.76 ± 1.42	1.7 ± 1.5	1.8 ± 1.4	.789

M, mean; SD, standard deviation; no., number. χ^2 tests were used for categorical variables. *T*-tests were used for continuous variables.

Table 2 Outcome measures for EMDR versus CAU.

	EMDR group (n=37)		CAU group (n=37)				
Outcome measure	**T1**	**T2**	**T1**	**T2**	***B*[a]**	***P*-value[b]**	**Effect size[c]**
Posttraumatic stress symptoms							
Child report							
Total PTSD score	45.00 ± 9.17	32.00 ± 11.80	44.37 ± 8.32	31.54 ± 11.76	-0.509	0.853	-.06
Intrusion	12.20 ± 4.19	8.29 ± 3.60	11.53 ± 3.08	7.50 ± 2.93	-0.044	0.966	-.01
Avoidance	18.77 ± 3.85	13.10 ± 5.32	18.69 ± 4.27	13.50 ± 5.06	-0.601	0.658	-.15
Hyperarousal	14.03 ± 4.11	10.61 ± 4.82	14.16 ± 4.30	10.54 ± 5.37	0.293	0.790	0.07
Parent report							
Total PTSD score	44.51 ± 10.80	32.94 ± 10.44	43.46 ± 9.78	35.43 ± 12.58	-3.468	0.275	-.34
Intrusion	11.86 ± 4.18	8.42 ± 3.64	11.14 ± 3.56	9.14 ± 3.80	-1.420	0.214	-.37
Avoidance	17.97 ± 5.12	13.58 ± 5.26	17.76 ± 4.91	14.37 ± 5.55	-1.038	0.482	-.21
Hyperarousal	14.68 ± 4.14	10.94 ± 3.42	14.57 ± 3.84	11.91 ± 4.81	-0.990	0.355	-.25
Symptoms of depression							
Child report	11.23 ± 6.04	6.17 ± 5.27	9.03 ± 6.38	7.07 ± 6.55	-2.473	0.037*	-.40
Parent report	17.59 ± 6.42	12.06 ± 6.03	14.65 ± 6.63	12.14 ± 7.20	-2.551	0.050	-.39
Symptoms of blood-injection-injury phobia							
Child report	6.31 ± 3.23	4.30 ± 2.83	5.16 ± 3.12	4.37 ± 3.20	-1.463	0.034*	-.46
Parent report	5.38 ± 3.06	4.52 ± 3.05	4.49 ± 3.05	4.17 ± 3.48	-0.541	0.364	-.18
Symptoms of anxiety							

Table 2 Continued

Outcome measure	EMDR group (n=37)		CAU group (n=37)		*B*[a]	*P*-value[b]	Effect size[c]
	T1	T2	T1	T2			
Child report	46.09 ± 22.87	28.73 ± 17.39	39.91 ± 16.86	29.63 ± 21.13	-6.834	0.101	-.34
Parent report	38.97 ± 16.76	27.39 ± 13.87	37.49 ± 20.43	30.43 ± 20.84	-3.833	0.288	-.20
Sleep problems							
Child report	38.63 ± 6.48	33.80 ± 6.04	35.41 ± 4.92	34.59 ± 6.80	-3.614	0.003*	-.63
Parent report	51.14 ± 8.61	46.12 ± 8.20	48.76 ± 7.96	47.35 ± 8.15	-2.751	0.032*	-.33

Mean ± standard deviation. *p <.05.
[a]GEE analyses. Uncorrected interaction of time x group.
[b]GEE analyses. P-values indicate level of significance of the uncorrected time x group interaction.
[c]Cohen's *d*.

Social validity
On a scale of 1 to 10, mean child (*n*=29) and parent (*n*=31) ratings of satisfaction with EMDR treatment were 8.2 (*SD*=1.6) and 8.0 (*SD*=1.1), respectively. The mean level of perceived usefulness of EMDR rated by children was 7.8 (*SD*=1.9) and by parents 6.8 (*SD*=2.3). On average, the willingness to recommend EMDR to others was rated with a 7.9 (*SD*=2.3) by children and with a 7.7 (*SD*=1.7) by parents.

DISCUSSION

This study presents outcomes of the first randomized controlled trial investigating the effectiveness of EMDR compared with CAU for children with medically related subthreshold PTSD after hospitalization for illness or injury. Children of both groups improved over time, but EMDR was superior in reducing symptoms of depression and BII phobia, and sleep problems.

We found significant improvements for both the EMDR and the CAU group over time on all outcomes. This could be due to the fact that children in the CAU group participated in a baseline psychological screening and an interview with a psychologist and, thereby, received additional attention from a professional. Participating in a structured assessment and hearing that PTSD symptoms were of subthreshold nature might be therapeutic in itself by acknowledging and normalizing the child's symptoms. Furthermore, research suggests that participating in a psychological study can decrease psychosocial symptomatology [51, 52].

With regard to PTSD symptom reduction, EMDR was as effective as CAU. This is in contrast to two meta analyses reporting on smaller studies [22, 24]. However, these studies did not specifically focus on medically related trauma and subthreshold PTSD. It is possible that with medically related subthreshold levels of PTSD, receiving attention from a mental health professional is enough to reduce symptoms and that EMDR, therefore, had no superior effect compared to CAU in our sample. Bearing in mind the limited resources of psychotherapists, a stepped-care model might be most efficient and cost-effective for monitoring and treating symptoms. This model proposes that mental health care is provided in steps and based on the needs of the child, with only those with persistent severe symptoms progressing to psychotherapy [53]. Additionally, natural remission from PTSD symptoms can also occur [14, 54]. Exact remission rates, however, of children with medically related subthreshold PTSD are unknown. Future research should provide

more insights into predictors of the EMDR treatment effect. It is important to note that we did not find any harmful effect of EMDR and that parents and children evaluated EMDR as very satisfactory.

Sleep problems are part of the DSM-V criteria for PTSD. However, sleep problems are rarely investigated as treatment outcome of EMDR. The present study presents support for the use of EMDR to reduce sleep problems in children after hospitalization. This is in line with Raboni et al. [30], who showed that EMDR treatment of PTSD improved sleep quality in adults.

Furthermore, PTSD tends to be closely related to specific phobias as these often have a traumatic origin too [55]. Interestingly, we found a superior effect of EMDR in reducing child-reported symptoms of blood-injection-injury phobia. This is in line with previous research indicating a positive effect of EMDR on dental phobia [56, 57]. Our finding that EMDR can reduce BII is clinically very relevant: it may be beneficial for future medical adherence as phobic patients tend to avoid the source of their fear.

Level of medical adherence has also been found to be smaller in patients who suffer from depression [58]. In line with previous findings, our results indicate that child-reported symptoms of depression decreased significantly more in the EMDR group than in the CAU group [28, 59] and, thereby, possibly improved medical adherence.

As to our multi-informant approach, correlations between child and parent report were moderate to high. Still, children reported significantly higher mean scores on BII phobia at T1 and sleep problems at T1 and T2 compared to parent-report. Earlier research has also found that child report tends to be higher than parent report on both outcomes [60, 61]. It has been argued that some aspects of internalizing problems and sleep may manifest beyond parent's awareness and therefore child-report might be more reliable [62, 63]. However this might not be true for young children. The additional analyses revealed that per-protocol analyses showed additional superior effects of EMDR on reducing child-reported anxiety and parent-reported symptoms of depression of the child. However, per-protocol analyses represents the best-case scenario and may therefore show an exaggerated effect [64]. Furthermore, we also tested whether the benefits of EMDR remained when the three erroneously randomized children were eliminated from the statistical analyses. The superior effects of EMDR on child-reported BII phobia and sleep

problems remained significant. Since results were changing during the additional analyses, results of this study should be interpreted with caution.

Finally, we also explored whether trauma type (I vs. II), type of department (emergency vs. cardiology) or time since last medical event (0-5 years) influence the found treatment effects. In accordance to Diehle et al. [35], treatment effect was not related to trauma type. The same was true for hospital department. However, the time elapsed since the last medical event did influence the treatment effect. The longer ago the last medical event happened, the more effective was EMDR in reducing child-reported symptoms of depression and sleep problems. This finding is explorative and should be tested in future studies.

Strengths and limitations

This study presents several strengths. First, our sample size was relatively large compared to earlier research into the effectiveness of EMDR in children. Second, we used parent and child report for all outcomes and included a broad age range. Third, we recruited participants throughout the Netherlands which increases generalizability. Fourth, all therapists received regular supervision and treatment integrity was assessed by multiple independent raters. Fifth, randomization was stratified and done by an independent researcher. Sixth, the researcher who was responsible for all assessments was blinded for randomization outcome. Finally, we specified the trauma type that children in our sample had experienced and explored the effects of trauma type during analyses.

Some limitations should also be noted. First, it should be noted that the CAU group did not represent real care-as-usual as this group received a psychological screening and interview in addition to regular medical care. No similar attention placebo control group was provided. Second, follow-up questionnaires were sent to participants 8 weeks after the first EMDR session regardless of whether EMDR was completed or not for methodological reasons. Therefore, the time between completion of EMDR and follow-up was different for every participant and six participants had not completed therapy when filling out the follow-up assessment. Third, EMDR might be more effective in children with more severe PTSD symptoms. However, it would have been unethical to randomize children with full diagnostic PTSD into a CAU group when other treatment options for PTSD are available. Fourth, due to the nature of EMDR it was not possible to blind participants to their group allocation. Finally, we did not assess parental mental health which is associated with parent report of the child's emotional wellbeing [65] and we did

not provide any treatment for parents. The effectiveness of EMDR might improve when an active parental treatment component would be added [27, 66].

Despite the mentioned possible limitations, this study represents the largest RCT up-to-date investigating the effectiveness of EMDR in children with medically related subthreshold PTSD after hospitalization.

Conclusion

In children with medically related subthreshold PTSD, EMDR and CAU performed similarly well at reducing PTSD symptoms. However, the present study provides some indication for the effectiveness of EMDR in reducing BII phobia, depression and sleep problems. No firm conclusions can be drawn from these findings since results changed during additional analyses. Comparable studies should be done to support the implementation of EMDR as an evidence-based therapy for BII phobia, depression and sleep problems after pediatric hospitalization.

DISCLOSURE STATEMENT

No potential conflicts of interest were reported by the authors.

FUNDING

This work was financially supported by Innovatiefonds Zorgverzekeraars, Stichting Hartekind, and Vereniging EMDR Nederland.

ACKNOWLEDGEMENTS

We thank all participating children and their parents/guardians and all involved therapists. Without them, this study would not have been possible.

REFERENCES

1. Kahana SY, Feeny NC, Youngstrom EA, Drotar D. Posttraumatic stress in youth experiencing illnesses and injuries: an exploratory meta-analysis. Traumatology. 2006; 12(2): 148-61.
2. Price J, Kassam-Adams N, Alderfer MA, Christofferson J, Kazak AE. Systematic review: a reevaluation and update of the integrative (trajectory) model of pediatric medical traumatic stress. J Pediatr Psychol. 2015: 1-10.
3. Pinquart M, Shen Y. Anxiety in children and adolescents with chronic physical illnesses: a meta-analysis. Acta Paediatr. 2011; 100(8): 1069-76.
4. Pinquart M, Shen Y. Depressive symptoms in children and adolescents with chronic physical illness: an updated meta-analysis. J Pediatr Psychol. 2010; 36(4): 375-84.
5. Lewandowski AS, Ward TM, Palermo TM. Sleep problems in children and adolescents with common medical conditions. Pediatr Clin. 2011; 58(3): 699-713.
6. Meentken MG, van Beynum IM, Legerstee JS, Helbing WA, Utens EMWJ. Medically related post-traumatic stress in children and adolescents with congenital heart defects. Front Pediatr. 2017; 5: 20.
7. Olofsson E, Bunketorp O, Andersson AL. Children and adolescents injured in traffic–associated psychological consequences: a literature review. Acta Paediatr. 2009; 98(1): 17-22.
8. De Bellis MD, Hooper SR, Woolley DP, Shenk CE. Demographic, maltreatment, and neurobiological correlates of PTSD symptoms in children and adolescents. J Pediatr Psychol. 2009; 35(5): 570-7.
9. Leskin LP, White PM. Attentional networks reveal executive function deficits in posttraumatic stress disorder. Neuropsychology. 2007; 21(3): 275.
10. Moradi AR, Taghavi R, Neshat-Doost HT, Yule W, Dalgleish T. Memory bias for emotional information in children and adolescents with posttraumatic stress disorder: a preliminary study. J Anxiety Disord. 2000; 14(5): 521-34.
11. Trickett PK, Noll JG, Putnam FW. The impact of sexual abuse on female development: Lessons from a multigenerational, longitudinal research study. Dev Psychopathol. 2011; 23(2): 453-76.
12. Carrion VG, Weems CF, Ray R, Reiss AL. Toward an Empirical Definition of Pediatric PTSD: The Phenomenology of PTSD Symptoms in Youth. J Am Acad Child Adolesc Psychiatry. 2002; 41(2): 166-73.
13. Zhang W, Ross J, Davidson JRT. Posttraumatic stress disorder in callers to the Anxiety Disorders Association of America. Depress Anxiety. 2004; 19: 96-104.
14. Cukor J, Wyka K, Jayasinghe N, Difede J. The nature and course of subthreshold PTSD. J Anxiety Disord. 2010; 24(8): 918-23.

15. Gutermann J, Schreiber F, Matulis S, Schwartzkopff L, Deppe J, Steil R. Psychological treatments for symptoms of posttraumatic stress disorder in children, adolescents, and young adults: a meta-analysis. Clin Child Fam Psychol Rev. 2016; 19(2): 77-93.

16. Dickstein BD, Walter KH, Schumm JA, Chard KM. Comparing response to cognitive processing therapy in military veterans with subthreshold and threshold posttraumatic stress disorder. J Trauma Stress. 2013; 26(6): 703-9.

17. Bisson JI, Roberts NP, Andrew M, Cooper R, Lewis C. Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults (Review). Cochrane Libr. 2013; (12).

18. Chen Y-R, Hung K-W, Tsai J-C, Chu H, Chung M-H, Chen S-R, et al. Efficacy of Eye-Movement Desensitization and Reprocessing for patients with Posttraumatic-Stress Disorder: A meta-analysis of randomized controlled trials. PLoS ONE. 2014; 9(8).

19. Seidler GH, Wagner FE. Comparing the efficacy of EMDR and trauma-focused cognitive-behavioral therapy in the treatment of PTSD: a meta-analytic study. Psychol Med. 2006; 36(11): 1515-22.

20. Herschell AD, McNeil CB, McNeil DW. Clinical child psychology's progress in disseminating empirically supported treatments. Clin Psychol. 2004; 11(3): 267-88.

21. Khan AM, Dar S, Ahmed R, Bachu R, Adnan M, Kotapati VP. Cognitive Behavioral Therapy versus Eye Movement Desensitization and Reprocessing in Patients with Post-traumatic Stress Disorder: Systematic Review and Meta-analysis of Randomized Clinical Trials. Cureus. 2018; 10(9).

22. Rodenburg R, Benjamin A, De Roos C, Meijer AM, Stams GJ. Efficacy of EMDR in children: A meta-analysis. Clin Psychol Rev. 2009; 29: 599-606.

23. Greyber LR, Dulmus CN, Cristalli ME. Eye Movement Desensitization Reprocessing, Posttraumatic Stress Disorder, and Trauma: A Review of Randomized Controlled Trials with Children and Adolescents. Child Adolesc Social Work J. 2012; 25(6).

24. Moreno-Alcázar A, Treen D, Valiente-Gómez A, Sio-Eroles A, Pérez V, Amann BL, et al. Efficacy of Eye Movement Desensitization and Reprocessing in Children and Adolescent with Post-traumatic Stress Disorder: A Meta-Analysis of Randomized Controlled Trials. Front Psychol. 2017; 8.

25. Lewey JH, Smith CL, Burcham B, Saunders NL, Elfallal D, O'Toole SK. Comparing the Effectiveness of EMDR and TF-CBT for Children and Adolescents: a Meta-Analysis. J Child Adolesc Trauma. 2018; 11(4): 457-72.

26. Valiente-Gómez A, Moreno-Alcázar A, Treen D, Cedrón C, Colom F, Perez V, et al. EMDR beyond PTSD: A systematic literature review. Front Psychol. 2017; 8: 1668.

27. De Roos C, Greenwald R, Den Hollander-Gijsman M, Noorthoorn E, van Buuren S, De Jongh A. A randomised comparison of cognitive behavioural therapy (CBT) and eye movement desensitisation and reprocessing (EMDR) in disaster-exposed children. Eur J Psychotraumatol. 2011; 2(1).

28. Bae H, Kim D, Park YC. Eye movement desensitization and reprocessing for adolescent depression. Psychiatry Investig. 2008; 5(1): 60.

29. Oras R, Ezpeleta SCd, Ahmad A. Treatment of traumatized refugee children with eye movement desensitization and reprocessing in a psychodynamic context. Nord J Psychiatry. 2004; 58(3): 199-203.

30. Raboni MR, Alonso FFD, Tufik S, Suchecki D. Improvement of mood and sleep alterations in posttraumatic stress disorder patients by eye movement desensitization and reprocessing. Front Behav Neurosci. 2014; 8.

31. Shapiro F. The Role of Eye Movement Desensitization and Reprocessing (EMDR) Therapy in Medicine: Addressing the Psychological and Physical Symptoms Stemming from Adverse Life Experiences. Perm J. 2014; 18(1): 71-7.

32. Kemp M, Drummond P, McDermott B. A wait-list controlled pilot study of eye movement desensitization and reprocessing (EMDR) for children with post-traumatic stress disorder (PTSD) symptoms from motor vehicle accidents. Clin Child Psychol Psychiatry. 2010; 15(1): 5-25.

33. Ribchester T, Yule W, Duncan A. EMDR for childhood PTSD after road traffic accidents: Attentional, memory, and attributional processes. J EMDR Pract Res. 2010; 4(4): 138-47.

34. Hassanzadeh Moghaddam M, Khalatbari J. Investigating the Effectiveness of Eye Movement Desensitization and Reprocessing (EMDR) on Children with Post-Traumatic Stress Disorder (Traffic Accident). Int J Indian Psychol. 2016; 3(3): 45.

35. Diehle J, Opmeer BC, Boer F, Mannarino AP, Lindauer RJL. Trauma-focused cognitive behavioral therapy or eye movement desensitization and reprocessing: What works for children with posttraumatic stress symptoms? A randomized controlled trial. Eur Child Adolesc Psychiatry. 2014; 24: 227-36.

36. Meentken MG, van Beynum IM, Aendekerk EWC, Legerstee JS, El Marroun H, van der Ende J, et al. Eye movement desensitization and reprocessing (EMDR) in children and adolescents with subthreshold PTSD after medically related trauma: design of a randomized controlled trial. Eur J Psychotraumatol. 2018; 9(1).

37. World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bulletin of the World Health Organization. 2001; 79(4): 373.

38. Alisic E, Eland J, Huijbregts RAD, Kleber RJ. Schokverwerkingslijst voor kinderen. Herziene handleiding. Diemen/Utrecht: Instituut voor Psychotrauma i.s.m. Klinisch & Gezondheidspsychologie (UU) en het Landelijk Psychotraumacentrum voor kinderen en Jeugd (UMC Utrecht); 2012.

39. Meentken MG, Van der Ende J, del Canho R, Van Beynum IM, Aendekerk EWC, Legerstee JS, et al. Psychological outcomes after pediatric hospitalization: the role of trauma type. Submitted for publication.

40. Lindauer RJ. Clinican administered PTSD scale for children and adolescents CAPS-CA. Klinisch interview voor PTSS bij kinderen en adolescenten. Houten: Bohn Stafleu van Loghum; 2014.

41. Gigengack MR, van Meijel EPM, Lindauer RJL. Diagnostic Infant and Preschool Assessment (DIPA). Nederlandse vertaling (concept/werkversie). Unpublished internal document.

42. Bodden D, Braet C, Stikkelbroek Y. CDI-2 Screeningsvragenlijst voor depressie bij kinderen en jongeren. Amsterdam: Hogrefe; 2016.

43. Muris PEHM, Bodden DHM, Hale WW, Birmaher B, Mayer B. SCARED-NL: Vragenlijst over angst en bang-zijn bij kinderen en adolescenten. Amsterdam: Boom test uitgevers; 2011.

44. Steur LMH, Grootenhuis MA, Terwee CB, Pillen S, Wolters NGJ, Kaspers GJL, et al. Psychometric properties and norm scores of the sleep self-report in Dutch children. Health Qual Life Outcomes. 2019; 17(1): 15.

45. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep. 2000; 23(8): 1043-52.

46. Landin-Romero R, Moreno-Alcazar A, Pagani M, Amann BL. How does eye movement desensitization and reprocessing therapy work? A systematic review on suggested mechanisms of action. Front Psychol. 2018; 9: 1395.

47. De Roos C, Beer R, de Jongh A, ten Broeke E. EMDR protocol voor kinderen en jongeren tot 18 jaar. Vereniging EMDR Nederland; 2013.

48. Lovett J. Small wonders: Healing childhood trauma with EMDR. New York: The Free Press; 1999.

49. Lovett J. Trauma-attachment tangle: modifying EMDR to help children resolve trauma and develop loving relationships. New York: Routledge; 2015.

50. Feingold A. Effect sizes for growth-modeling analysis for controlled clinical trials in the same metric as for classical analysis. Psychol Methods. 2009; 14(1): 43.

51. McCambridge J. From question-behaviour effects in trials to the social psychology of research participation. Psychol Health. 2015; 30(1): 72-84.

52. Arrindell WA. Changes in waiting-list patients over time: data on some commonly-used measures. Beware! Behav Res Ther. 2001; 39(10): 1227-47.

53. Marsac ML, Hildenbrand AK, Kassam-Adams N. Interventions in medical settings. Evidence-based treatments for trauma related disorders in children and adolescents: Springer; 2017. p. 405-25.

54. Smith P, Yule W, Perrin S, Tranah T, Dalgleish TIM, Clark DM. Cognitive-behavioral therapy for PTSD in children and adolescents: a preliminary randomized controlled trial. J Am Acad Child Adolesc Psychiatry. 2007; 46(8): 1051-61.

55. McNally RJ, Saigh PA. On the distinction between traumatic simple phobia and posttraumatic stress disorder. Posttraumatic stress disorder: DSM-IV and beyond. 1993: 207-12.

56. Doering S, Ohlmeier MC, de Jongh A, Hofmann A, Bisping V. Efficacy of a trauma-focused treatment approach for dental phobia: a randomized clinical trial. Eur J Oral Sci. 2013; 121(6): 584-93.

57. De Jongh A, Van den Oord HJM, Ten Broeke E. Efficacy of eye movement desensitization and reprocessing in the treatment of specific phobias: Four single-case studies on dental phobia. J Clin Psychol. 2002; 58(12): 1489-503.

58. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: Meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000; 160(14), 2101–7.

59. De Roos C, Van der Oord S, Zijlstra B, Lucassen S, Perrin S, Emmelkamp P, et al. EMDR versus Cognitive Behavioral Writing Therapy versus Waitlist in Pediatric PTSD Following Single-Incident Trauma: A Multi-Center Randomized Clinical Trial. Journal of Child Psychology and Psychiatry. 2017.

60. Wren FJ, Bridge JA, Birmaher B. Screening for childhood anxiety symptoms in primary care: integrating child and parent reports. J Am Acad Child Adolesc Psychiatry. 2004; 43(11): 1364-71.

61. Owens JA, Spirito A, McGuinn M, Nobile C. Sleep habits and sleep disturbance in elementary school-aged children. J Dev Behav Pediatr. 2000; 21(1): 27-36.

62. Becker SP. External validity of children's self-reported sleep functioning: associations with academic, social, and behavioral adjustment. Sleep Med. 2014; 15(9): 1094-100.

63. Cosi S, Canals J, Hernández-Martinez C, Vigil-Colet A. Parent–child agreement in SCARED and its relationship to anxiety symptoms. J Anxiety Disord. 2010; 24(1): 129-33.

64. Ranganathan P, Pramesh CS, Aggarwal R. Common pitfalls in statistical analysis: Intention-to-treat versus per-protocol analysis. Perspect Clin Res. 2016; 7(3): 144.

65. Shemesh E, Newcorn JH, Rockmore L, Shneider BL, Emre S, Gelb BD, et al. Comparison of parent and child reports of emotional trauma symptoms in pediatric outpatient settings. Pediatrics. 2005; 115(5): 582-9.

66. Cobham VE, March S, De Young A, Leeson F, Nixon R, McDermott B, et al. Involving parents in indicated early intervention for childhood PTSD following accidental injury. Clin Child Fam Psychol Rev. 2012; 15(4): 345-63.

7

CHAPTER 7

General discussion

GENERAL DISCUSSION

The overall focus of the current thesis was to examine and improve the psychosocial well-being of children with congenital or acquired heart defects. The main aims were to study:

(1) whether anxiety problems in young children with anxiety disorders decreased after participating in the Fun FRIENDS program;
(2) the effectiveness of the CHIP-Family intervention on the psychosocial well-being of young children with congenital heart defects (CHDs) and their families;
(3) the level of emotional and behavioral problems in children with dilated cardiomyopathy (DCM);
(4) the effectiveness of eye movement desensitization and reprocessing (EMDR) in children with medically-related subthreshold posttraumatic stress disorder (PTSD).

The main aims, methods, and findings are summarized in Table 1. In the following section, our findings are summarized and placed in a broader perspective. We will also discuss the implications of our findings for the development of future psychosocial interventions in this population, suggest directions for future research, and discuss clinical implications.

FUN FRIENDS PROGRAM FOR YOUNG CHILDREN WITH ANXIETY DISORDERS

In chapter 2, we described our explorative pilot study examining whether anxiety symptoms in 28 children with anxiety disorders decreased after participating in the Dutch version of the cognitive behavioral (CBT) Fun FRIENDS program. From pre-intervention to direct post-intervention, we found a significant decrease in anxiety problems, the mean number of anxiety disorders, symptom interference, and overall emotional and behavioral problems. These results are in line with previous findings of Fun FRIENDS trials in clinical settings [1-3].

We also examined whether gender, age, and level of pre-intervention anxiety problems predicted treatment progress. We found that a higher level of pre-intervention anxiety problems predicted more treatment progress, but gender and age did not appear to be significant predictors. Though the results of previous studies are inconsistent, a systematic review has shown that most studies have

failed to find significant demographic or clinical predictors of treatment progress and outcome in children with anxiety disorders [4].

We did not find significant decreases as to externalizing problems. As the main aim of the Fun FRIENDS program is to decrease and/or prevent internalizing problems such as anxiety and depression [5], it is not surprising that externalizing problems did not significantly decrease from pre-intervention to post-intervention. Moreover, the participating children were primarily referred for treatment because of anxiety problems and had pre-intervention levels of externalizing problems comparable to normative data, which makes significant improvements in this domain neither likely nor necessary.

Research into anxiety problems in preschoolers has only emerged in the past decade. At the start of this project, the Fun FRIENDS program was the only available standardized intervention for young children with anxiety disorders in the Netherlands. Our study and previous studies examining Fun FRIENDS yielded promising results as to treatment progress of children with anxiety problems. Because children with a CHD are especially at increased risk of internalizing problems [6], we reasoned that a psychosocial intervention for this population should include exercises aimed at decreasing anxiety. Therefore, we incorporated exercises of the Fun FRIENDS program into the child module of the CHIP-Family program.

CHIP-FAMILY INTERVENTION FOR YOUNG CHILDREN WITH CHDS AND THEIR FAMILIES

Chapter 3 presents the trial design of our study into the effectiveness of the CHIP-Family intervention. The previously developed and investigated CHIP-School program aimed to indirectly improve the psychosocial well-being of young children with CHD by providing a psychosocial intervention for their parents [7]. Though CHIP-School showed promising results, we aimed to improve the effects of the intervention by innovating the program and by adding a specific child module for children with CHD and a sibling or friend. We expected that targeting the child directly and including family members would optimize the effects of the intervention.

Table 1 Summary of main aims and main findings of this thesis.

Chapter	Short title	Aim	Sample	Methods	Main findings
2	CBT for anxiety disorders in young children: the Fun FRIENDS program	To examine whether young children with anxiety disorders showed less anxiety after participating in Fun FRIENDS.	*n*=28 children with anxiety disorders (4-8 years old, *M*=6.6, *SD*=1.1)	Design: Retrospective open trial. T1: pre-intervention T2: direct post-intervention Parent-report measures: · ADIS-C: number of anxiety disorder diagnoses, symptom interference · CBCL: emotional and behavioral problems	Statistically significant decreases from pre-intervention to post-intervention in: · number of anxiety disorders; · symptom interference; · overall emotional and behavioral problems; · internalizing problems; · and anxiety problems. Non-significant decreases in: · anxious/depressed problems; · and externalizing problems. Higher pre-intervention anxiety levels predicted more treatment progress. Gender and age did not.
3	CHIP-Family for young children with CHD and their families: trial design	To describe the rationale and content of the CHIP-Family intervention and the design of the RCT into the effectiveness CHIP-Family; a multidisciplinary psychosocial intervention for young children with CHD and their families.	Children eligible for participation in the RCT are described in this chapter.	The design and measures of the RCT are described in this chapter.	Not applicable.

Table 1 Continued

Chapter	Short title	Aim	Sample	Methods	Main findings
4	CHIP-Family for young children with CHD and their families: results	To examine the effectiveness of the CHIP-Family intervention in improving psychosocial well-being of young children with CHD and their families.	*n*=93 children with CHD (3-8 years old, *M*=5.34, *SD*=1.27)	Design: Single-blinded randomized trial with CAU control group. T1: pre-intervention T2: 6-month follow-up Primary parent-report measures: · CBCL: emotional and behavioral problems · SCL-90-R: parental mental health	· At 6-month follow-up, child and parent outcomes of the CHIP-Family and CAU group did not significantly differ. · Parents rated the CHIP-Family intervention positively.
5	Emotional and behavioral problems in children with DCM	To investigate in children with DCM: · the level of emotional and behavioral problems compared to normative data; · anxiety and depressive problems predict the combined risk of death or cardiac transplantation.	*n*=68 children with DCM (1.5-18 years old, *M*=6.87, *SD*=5.72)	Design: Observational cross-sectional study One assessment Parent-report and medical measures: · CBCL: emotional and behavioral problems · NYU PHFI: heart failure severity · Endpoint: mortality and cardiac transplantation	Compared to normative data: · more young (1.5-5 years) children with DCM showed somatic complaints; · less young children with DCM showed externalizing problems. Compared to normative data, more older (6-18 years) children with DCM showed: · overall internalizing problems; · depressive problems; · anxiety problems; · and somatic complaints. Whereas heart failure severity predicted the combined risk of death or cardiac transplantation, anxiety and depressive problems did not.

Table 1 Continued

Chapter	Short title	Aim	Sample	Methods	Main findings
6	EMDR for children with medically-related subthreshold PTSD: short-term effects	To determine the short-term effectiveness of EMDR in children with subthreshold PTSD after hospitalization.	*n*=74 children with medically-related subthreshold PTSD (4-15 years old, *M*=9.6, *SD*=2.9)	Design: Single-blinded randomized trial with CAU control group. T1: pre-intervention T2: 2 months after baseline Parent- and child-report measures: · CRTI: PTSD symptoms · CDI-2: depression symptoms · SCARED-NL: blood-injection-injury phobia, anxiety · SSR & CSHQ: sleep problems	Children in the EMDR and the CAU group improved significantly over time on all outcomes. Children in the EMDR group improved significantly more than the CAU group regarding: · child-reported symptoms of blood-injection-injury phobia; · child-reported depression; · child- and parent-reported sleep problems of the child.

Abbreviations: ADIS-C = Anxiety Disorders Interview Schedule for DSM-IV - Child Version; CAU = care as usual; CBCL = Child Behavior Checklist; CBT = cognitive behavioral therapy; CDI-2 = Children's Depression Inventory 2; CHD = congenital heart defects; CHIP = Congenital Heart Disease Intervention Program; CRTI = Children's Responses to Trauma Inventory; CSHQ = Children's Sleep Habits Questionnaire; DCM = dilated cardiomyopathy; EMDR = eye-movement desensitization and reprocessing; NYU PHFI = New York University Pediatric Heart Failure Index; PTSD = Posttraumatic Stress Disorder; RCT = randomized controlled trial; SCARED-NL = Screen for Child Anxiety Related Disorders, Dutch version; SCL-90-R = Symptom Checklist-90-Revised; SSR = Sleep Self-Report; T1 = first assessment moment; T2 = second assessment moment.

To the best of our knowledge, CHIP-Family is the first standardized psychosocial intervention for young children with CHD which includes a specific child module. As mentioned above, the child module contained CBT exercises based on the Fun FRIENDS program. These CBT exercises were provided by two trained junior psychologists. The child module also contained sports exercises provided by a pediatric physiotherapist and a physiotherapy assistant. In the parent module, parents discussed and practiced problem prevention therapy, general parenting skills, parenting skills specific to children with CHD, and related medical issues. The parent module was provided by two senior clinical psychologists with expertise in CHD and a pediatric cardiologist. All parent couples received a follow-up session with a psychologist who was present at the child workshop and a psychologist who was present at the parent workshop. In the follow-up session, parent couples discussed any remaining questions or worries, the most helpful components of the program, future coping strategies, and the problem prevention home assignment.

Chapter 4 presents the results of our randomized controlled trial (RCT) into the effectiveness of CHIP-Family on parental mental health, children's emotional and behavioral problems, and family functioning. We compared CHIP-Family to care as usual (CAU; regular medical care only). In total, we provided 11 workshops and corresponding individual follow-up sessions. We found that, compared with CAU, participation in the CHIP-Family program did not result in significant improvements at 6-month follow-up as to child and parental psychosocial well-being and family functioning. In addition, father-reports and mother-reports of children's emotional and behavioral problems did significantly improve in both the CAU and the CHIP-Family group.

These improvements in emotional and behavioral problems in both groups may have been caused by merely participating in the study. That is, it can be debated whether participants in the CAU condition actually received CAU, because all participants received information and additional attention (explained below) from professionals which is generally not part of standard practice. Usually, children with CHD are only referred for mental health care if psychosocial problems are noticed by their pediatric cardiologist or if parents themselves explicitly indicate a need for care. However, prior to participation in the CHIP-Family RCT, eligible families received an information letter explaining the rationale of the study, which can be considered as encompassing psychoeducation. All families also received at least one phone call from the researchers and, prior to participation, some parents discussed the study with their child's pediatric cardiologist. Furthermore,

parents in both the CAU and the CHIP-Family group completed questionnaires at baseline and follow-up. Previous research has described that simply completing a questionnaire can influence subsequent behavior: a phenomenon described as the 'question-behavior effect' [8]. The baseline assessment may have increased parents' awareness of emotional and behavioral problems. Subsequently, they may have attempted to decrease these problems [9], which may have resulted in decreased scores at follow-up. Similar result patterns have been reported in previous RCTs in other pediatric chronic illnesses such as inflammatory bowel disease [10-12]. Relatedly, the results may have been influenced by the test-retest effect [9]. That is, from pre-test to post-test, mean scores of psychosocial problems often decrease, even without an intervention.

Despite randomization (stratified for age and CHD severity), we found that, at baseline, mothers from the CHIP-Family group reported more emotional and behavioral problems in their children than mothers from the CAU group. Since participants were randomly allocated to either group, this finding was unexpected. However, for methodological and practical reasons, parents were aware of randomization outcome prior to completing the baseline assessment, which may have influenced the results. That is, in order to limit the period between a family's baseline assessment and participation in the CHIP-Family workshop to two weeks, we had to ask families whether they would be able to attend the program on a specific date. Parents also had to make practical arrangements at work (take a whole day off) and at their children's school in advance. As a result of being aware of randomization outcome, mothers randomized into the CHIP-Family group may have prepared for the program by reflecting and focusing more on their children's problems, which may have increased their reports of emotional and behavioral problems in their child.

Next to standardized outcome measures, we assessed parents' satisfaction regarding CHIP-Family through a specific questionnaire developed to this end. Parents were highly satisfied with the program and scored its usefulness positively. They considered the psychosocial and medical explanation by a pediatric cardiologist, meeting other families, and the child workshop to be the most valuable components of the program. The majority of participating parents had a high educational level and most parents who participated in the CHIP-Family program mentioned that they had already searched for information on CHD and parenting skills. Nevertheless, parents were very satisfied with the program. On the other

hand, highly motivated parents may tend to be more positive as to the program's usefulness and satisfaction, which may have induced bias.

Importantly, in four children who participated in the CHIP-Family program, parents and the psychologists indicated a need for additional psychosocial care. Subsequently, our team referred these children for further psychological care. In contrast, we did not refer any children from the CAU group for further care. This indicates that CHIP-Family facilitated mental health care professionals and parents to detect psychosocial problems in children. Without CHIP-Family, these problems may have remained unnoticed. This is clinically relevant, because detecting and treating psychosocial problems at an early stage may prevent the development of chronic disorders and more severe problems [13-15]. An alternative explanation could be that children in the CHIP-Family group experienced more problems than children in the CAU group, which may also be reflected by the higher level of baseline emotional and behavioral problems reported by mothers in the CHIP-Family group compared with the CAU group. Overall, the previously examined CHIP-School yielded more positive results than CHIP-Family [7]. Nevertheless, the results of the CHIP-Family RCT offer valuable information. Replicating studies is central to any science [16]. Unfortunately, studies examining the effect of psychological interventions in children with a CHD are very scarce, let alone replication studies [17]. This scarcity could be increased by publication bias: scientific journals tend to publish more studies reporting statistically significant results than studies reporting non-significant or opposite results [18, 19]. This is unfortunate, because replication studies provide information on which ingredients are valuable in improving interventions – also when results are not statistically significant.

Below, we discuss which ammunition the results of the CHIP-Family RCT provide to further refine psychosocial interventions for children with a CHD regarding the following questions:

- Target group: who should receive a psychosocial intervention?
- Content: what should the intervention entail?
- Mode of delivery: how should the intervention be provided?
- Timing: when should the intervention be provided?

Target group

In pediatric chronic illness, it is well-established that parental mental health influences children's psychosocial well-being [e.g., 20, 21-23]. Moreover, chronic illness such as CHD affects the whole family [24-28]. For these reasons, family-centered psychosocial interventions are commonly recommended nowadays [29]. Though family-related topics were discussed, the previously examined CHIP-School intervention only included a parent program [7]. By providing a psychosocial intervention for parents, the developers aimed to indirectly improve child outcomes [23]. As mentioned, in developing CHIP-Family, we hypothesized that adding a specific child module would further improve child outcomes. Interestingly, the results of our RCT examining the CHIP-Family program did not support this hypothesis. CHIP-School yielded more positive outcomes than CHIP-Family on parent, family, and child outcomes. An explanation for this might be that, in CHIP-Family, parent workshops and child workshops were held simultaneously. Parents considered the child workshop to be one of the three most valuable components of CHIP-Family. However, involving children in the workshop may have reduced parents' focus on and perceived importance of the parent module of CHIP-Family. This seems to indicate that including both parents and children in a psychosocial intervention does not necessarily improve outcomes. As demonstrated by a recent meta-analysis, it is currently unknown whether the effect of psychosocial interventions can be improved by including not only parents, but also the child itself [20].

Furthermore, one might expect that children with more severe CHDs require more psychosocial care. However, this does not appear to be the case. A meta-analysis has shown that emotional and behavioral problems are not related to illness severity [6]. In the CHIP-Family workshops, parents of children with different types of CHD reported that they experienced similar difficulties, regardless of the severity of residual heart defects.

Content

In developing a psychosocial intervention for children with CHD, several treatment classes can be considered. The parent module of CHIP-Family and CHIP-School mainly consisted of problem prevention therapy (PPT) and CBT. Previous meta-analyses examining psychosocial interventions targeting parents of chronically ill children have found beneficial results on parental outcomes of PPT and of CBT [20, 30, 31]. The child module of CHIP-Family primarily consisted of CBT exercises from the Fun FRIENDS program. Parents who participated in CHIP-Family considered

the information as to psychosocial and medical topics provided by the pediatric cardiologist and discussing these topics with other families to be the most valuable components of the program. During the explanation of the pediatric cardiologist, questions and discussions were stimulated and coached by two senior clinical psychologists with expertise in the field. Two senior psychologists were present the whole day, which enabled them to gather parents' questions throughout previous parts of the workshop program.

As to CHIP-School, however, parents considered the bicycle exercise stress test to be the most valuable component [personal communication with the developers of CHIP-School]. The bicycle exercise stress test was a behavioral experiment in which the child was encouraged to perform vigorous exercise whilst being monitored by a cardiologist. Parents were present and were assured by the cardiologist that the heart rhythms monitored through the electrocardiogram were non-concerning throughout the exercise. For logistical reasons, this component could not be implemented in the CHIP-Family program. As mentioned, however, CHIP-Family did include sports exercises developed and supervised by a pediatric physiotherapist. Though parents attended part of this sports program, this may not have had the same reassuring effect as the bicycle exercise stress test in the presence of a cardiologist. Clearly, parents appreciated the involvement of professionals from multiple disciplines in CHIP-Family and CHIP-School. This is valuable, as children with chronic illnesses such as CHD face a broad range of difficulties [29, 32].

The duration of the intervention may also affect outcomes. Both the CHIP-School and CHIP-Family program are relatively brief interventions. This can be considered a strength, as this minimizes the burden of treatment for participants and the time investment required of the involved professionals. However, to further improve outcomes, an intervention of a longer duration may be needed. As mentioned above, the Fun FRIENDS program showed promising results in a clinical setting. Fun FRIENDS consists of 12 weekly 1.5-hour sessions, whereas the CBT component of the CHIP-Family child program was merged into one 4 hour session. If CBT exercises are practiced repeatedly, it is more likely that lasting improvements will be obtained.

It should also be recalled that, in the CHIP-Family RCT, parents in both the CAU and the CHIP-Family group did report improvements from baseline to 6-month follow-up in children's emotional and behavioral problems. This suggests that merely receiving psychoeducation may be sufficient in improving outcomes.

Mode of delivery

The CHIP-Family intervention was provided face-to-face. The workshops were provided in a group format. As previously noted, parents rated meeting other families of children with a CHD as one of the most valuable aspects of the CHIP-Family program. Parents appreciated the opportunity to discuss issues with parents who had gone through similar experiences. Formulated by some as an "eye-opener", sharing similar experienced may have a normalizing effect. In CHIP-Family, workshop group sizes were smaller (3 to 5 families, 4 to 10 parents) than in CHIP-school (9 to 12 parents). We expected that smaller group sizes would enable more personal attention and, therefore, enhance impact. However, on the other hand, larger group sizes may also increase the support impact of the group format.

Though the group format of CHIP-Family was highly appreciated, alternative modes of intervention delivery could also be considered. As stated in the previous section, receiving psychoeducation seems to improve children's outcomes. Within this framework, an online evidence-based patient information portal may be of value. A previous pilot study has shown that patients with CHD appreciate and apply such an information portal [33]. A multicenter stepped-wedge trial examining the effects of this information portal for cardiac patients is currently being conducted at the Erasmus MC.

Timing

Intervening at a young age has several advantages. Problem behaviors and thoughts may be easier to modify, as problems may be less ingrained and neuroplasticity of young children is higher [34]. Moreover, if left untreated, psychosocial problems may become chronic and persist into adolescence and adulthood [35, 36]. Providing an effective early intervention can minimize the impact of psychosocial problems on the development and future life of a child [34, 37-39]. Indeed, previous studies [1-3] and our results regarding the Fun FRIENDS program suggest that early intervention can be effective.

According to Drotar [40], psychosocial interventions should be provided at times of developmental transitions. For this reason, CHIP-School targeted families of children who were entering school. CHIP-Family included families of children who were starting preschool or kindergarten. Some participating children had already entered preschool or kindergarten. Perhaps CHIP-Family would have obtained more favorable results if all participating children were at the start of the developmental transition of entering school. Participating parents did confirm

that developmental transitions pose additional challenges for their families. Furthermore, parents often mentioned that they would have appreciated an intervention such as CHIP-Family earlier in the illness trajectory. According to parents, they had already dealt with the most severe difficulties. However, evidence also indicates that a psychosocial intervention should not be provided too early: a psychosocial intervention for parents of children with cancer was effective when delivered later in the illness trajectory, but did not prove to be as successful earlier in the illness trajectory [41].

EMOTIONAL AND BEHAVIORAL FUNCTIONING IN PEDIATRIC DCM

In chapter 5, we examined the proportion of borderline and clinical emotional and behavioral problems in a cohort of children with DCM compared to the general population. Though multiple cross-sectional and cohort studies have examined emotional and behavioral functioning in pediatric CHD, such studies in pediatric DCM are scarce. In our study, we found that, compared to normative data [42], a significantly smaller proportion of young children (i.e., 1.5- to 5-year-olds) with DCM showed externalizing problems (5.4% versus 17.0%) and a significantly larger proportion of young children showed somatic complaints (24.3% versus 8.0%). Moreover, compared to normative data [42], a significantly larger proportion of older children (i.e., 6- to 18-year-olds) with DCM showed internalizing problems (38.7% versus 17.0%), including depressive, anxiety, and somatic problems.

Only two small previous studies have examined emotional and behavioral problems in pediatric cardiomyopathy. The first study [43] (n=19) included 3.7- to 14.2-year-old children with cardiomyopathy who were listed for cardiac transplantation. Half of all participants showed a clinical level of overall emotional and behavioral problems as reported by parents on the CBCL. In our study, this proportion was much smaller for both 1.5- to 5-year-olds (10.8%) and 6- to 18-year-olds (16.1%). Presumably, being listed for cardiac transplantation increased the level of emotional and behavioral problems in the previous study. This increase could be due to elevated uncertainty as to prognosis and treatment [44, 45]. Also, anxiety and depressive symptoms in children listed for cardiac transplantation may be increased because they experience more physical symptoms of their illness [44, 46] and may have to undergo more frequent and more intensive medical treatments [47]. Furthermore, it is well-known that parental mental health influences the psychosocial well-being of the affected child [20-23, 48]. We hypothesize that

parents of children listed for cardiac transplantation experience increased levels of anxiety which subsequently can increase the child's level of emotional and behavioral problems. In interpreting the results of this study, the small sample size should be taken into account.

The second previously published study [49] (n=15) included 7- to 21-year-old children and adolescents with DCM. Contrary to our results, this study found that the level of depressive problems did not differ between children with DCM, healthy children (n=24), and children who had successfully undergone cardiac transplantation for heart failure (n=23). Again, in interpreting these results, the small sample size should be taken into account. In addition to a different age range, this study used the CDI to assess depressive problems, whereas we used the CBCL. Importantly, the CDI was completed by the participating children themselves, whereas the CBCL is a caregiver-report questionnaire.

Besides examining the level of emotional and behavioral problems in DCM, we investigated whether depressive and anxiety problems predicted cardiac transplantation and mortality, independent from heart failure severity. Whereas heart failure severity did appear to predict cardiac transplantation and mortality, depressive and anxiety problems did not. This result was unexpected, because in adult heart failure populations, multiple studies have shown that depressive and anxiety problems predict adverse clinical outcomes and mortality [50, 51]. Depressive and anxiety problems in adults can diminish self-care and health behaviors, subsequently placing adults with heart failure at risk for adverse outcomes [52]. Regarding pediatric DCM, parents may put efforts in reducing depressive and anxiety problems and may compensate for children's diminished self-care, subsequently reducing the risk for adverse outcomes in these children.

Our findings indicate that a psychosocial intervention may be needed for children with DCM. However, considering the scarcity of studies examining the psychosocial well-being of these children, more research is needed before firm conclusions can be drawn. Future research should examine the level of psychosocial problems in children with DCM and determine the content of a psychosocial intervention. Since children with DCM seem to suffer from internalizing problems (i.e., anxiety and depression), we recommend to investigate the effectiveness of CBT interventions, as CBT is the treatment of first choice for children with internalizing problems [53, 54].

EMDR IN MEDICALLY-RELATED SUBTHRESHOLD PTSD

In chapter 6, we conducted an RCT to investigate the effectiveness of EMDR in children with medically-related subthreshold PTSD compared to CAU (regular medical care only). We included children with CHD, children with acquired heart defects, and children who had been admitted to an emergency department. All participating children were required to have been admitted to a hospital for at least one night. This is the first study examining the effect of EMDR in children with CHD. Approximately 2 months after the start of EMDR or CAU, we found that children in both the CAU and the EMDR intervention group significantly improved on posttraumatic stress symptoms, general anxiety, blood-injection-injury phobia, depression, and sleep problems. The finding that both groups improved over time may be attributed to the phenomenon that merely participating in a study may result in better psychosocial outcomes (as described above in the section discussing the CHIP-Family study). All eligible patients received an information letter explaining the content of the study. This information letter also contained psychoeducational information on consequences of a hospital admission and traumatic events. Furthermore, before inclusion in the EMDR RCT, potential participants were screened for PTSD symptoms and completed a semi-structured interview with a psychologist. Participants were screened because only children with subthreshold PTSD were included in the RCT. Psychoeducation or attention from a psychologist might be sufficient to decrease problems in children with subthreshold PTSD. That is, following a potentially traumatic medical event, it may be sufficient for a number of children to receive an information letter and a phone call from a mental health care professional providing psychoeducation. Within this framework, the previously mentioned online evidence-based patient information portal may provide a valuable format [33].

Compared to the CAU group, children in the EMDR group did significantly improve on self-reported symptoms of blood-injection-injury phobia and depression, and on parent-reported and child-reported sleep problems of the child. EMDR did not result in more favorable outcomes as to PTSD symptom reduction. Most of our results are in line with previous research [55-59]. In contrast to earlier studies, EMDR did not prove superior in reducing PTSD symptoms. Two meta-analyses reporting on small RCTs did find a superior effect of EMDR on PTSD symptoms compared with CAU, a waitlist, or a non-established trauma treatment [60, 61], whereas we did not. A possible explanation for this discrepancy is that the studies included in the meta-analyses also targeted children and adolescents with clinically

diagnosed PTSD who likely experienced higher levels of symptom severity than the children included in our RCT.

In an exploratory analysis, we found that outcomes as to child-reported symptoms of depression and sleep problems in the EMDR group were more favorable if more time had elapsed since the last medical event. Nevertheless, some adult studies advocate early EMDR intervention after trauma [62]. The best time to provide EMDR to children with medically-related trauma remains to be investigated.

Again, next to standardized outcome measures, we assessed children's and parents' satisfaction with the EMDR treatment. Overall, treatment satisfaction and usefulness were evaluated positively. In the CHIP-Family workshop groups, multiple parents reported that they had successfully received EMDR themselves for their own posttraumatic stress symptoms (PTSS) or PTSD due to medical events of their child [26].

STRENGTHS AND LIMITATIONS

The strengths and limitations of the studies described in this thesis have been discussed extensively in the previous chapters. In short, the single-blind RCTs described in this thesis add to the limited evidence-based knowledge body concerning psychosocial interventions for children with heart defects. Treatment integrity was high, as were parents' satisfaction ratings. Worldwide, our RCT into CHIP-Family was the first to examine a psychosocial intervention for CHD including a specific child module. Also, fathers were actively involved in the intervention and completed assessments, which is rare in pediatric research [20, 63, 64]. The EMDR study was the first study to examine the effectiveness of EMDR in children with CHD-related and other medically-related subthreshold PTSD. Moreover, this study included reports from multiple informants and had a relatively large sample size considering previous studies into EMDR for children. Participants for the EMDR and CHIP-Family study were recruited in multiple centers across the Netherlands, which increases the generalizability of the results. Furthermore, our study on the Fun FRIENDS program was the first study examining this program in a European sample of young children with anxiety disorders. We also examined emotional and behavioral problems in a substantial cohort of children with DCM; a largely unexplored field. Children of all ages were recruited in seven hospitals across the Netherlands, again increasing the generalizability of our results.

A number of limitations should also be considered. In our studies examining Fun FRIENDS, CHIP-Family, and emotional and behavioral problems in children with DCM, we primarily used parent-proxy reports. Though the use of parent-proxy reports is common within the field of pediatric psychology, this can be considered a methodological limitation as agreement among different informants generally is found to be moderate [65-69]. Furthermore, though the sample sizes of our studies were relatively large considering previous studies and prevalence rates, the sample sizes may have compromised statistical power and subsequently increased the chance of type II errors (i.e., false negatives). Moreover, as discussed above, parents in the CHIP-Family trial were aware of randomization outcome prior to the baseline assessment, which may have influenced the results. Besides, we may have found more favorable outcomes if we had included children with more severe psychosocial problems in the CHIP-Family and EMDR studies. However, it would have been unethical to randomize children with a clinical level of problems into a CAU group.

DIRECTIONS FOR FUTURE RESEARCH

Future research should be conducted on the Fun FRIENDS program, psychosocial interventions for children with heart defects, and the psychosocial functioning of children with DCM. We incorporated elements of the Fun FRIENDS program into the CHIP-Family program to decrease internalizing problems in children with CHD. However, regarding Fun FRIENDS as a treatment program for young children with anxiety disorders, randomized controlled trials with adequate sample sizes are needed to draw definite conclusions on its effectiveness. This is important, as early intervention can prevent the development of more severe, chronic problems [34-39] and our and previous Fun FRIENDS trials show promising results [1-3].

Regarding psychosocial interventions for children with heart defects and their families, four recommendations for future research can be postulated. Firstly, most studies on psychosocial problems in pediatric heart defects are cross-sectional studies. Despite the fact that international guidelines have advocated that psychosocial care should be incorporated in standard clinical practice for CHD [70], studies aimed at developing and testing the effectiveness of interventions are still lacking and should be initiated and executed. Secondly, the added value of including a child module in a psychosocial intervention for pediatric heart disease should be further examined [20]. Thirdly, research should identify which children and families could benefit sufficiently from psychoeducation alone and which

children and families require additional psychosocial care. Fourthly, the timing of providing EMDR therapy should be investigated in children with medically-related (subthreshold) PTSD. Our results showed some indications that time elapsed since the event was positively related with outcomes.

As current psychosocial research in children with DCM is limited to health-related quality of life, many questions remain to be answered. Firstly, we examined parent-reports of emotional and behavioral functioning of children with DCM. It would be valuable to examine children's own experiences as well. Secondly, studies should investigate whether disease severity in pediatric DCM is related to the level of emotional and behavioral problems. This information would help to identify which children are in need of a psychosocial intervention. Thirdly, we examined the difference in emotional and behavioral problems in younger (i.e., 1.5 to 5-year-olds) and older (i.e., 6 to 18-year-olds) children with DCM. Again, to identify children at risk for psychosocial problems, it would be valuable to examine age differences in more detail. Fourthly, though our study comprised a substantial sample size considering the prevalence of pediatric DCM, studies with larger sample sizes are required to increase statistical power and generalizability of results. Fifthly, researchers may consider conducting a qualitative study to examine the psychosocial well-being of children with DCM and potential difficulties they experience.

As to pediatric psychology in general, researchers should aim to establish consensus on which illness-specific and general measurement instruments should be used. The heterogeneity of used measurement instruments complicates the comparison of results. Often, it is unclear whether differences in outcomes reflect actual differences or differences in specificity or sensitivity of assessment instruments.

CLINICAL IMPLICATIONS AND RECOMMENDATIONS

- Early intervention by means of the Fun FRIENDS program for young children with anxiety disorders can be beneficial. Its effectiveness in clinical settings remains to be further established through an RCT.
- We recommend structural screening through questionnaires for children with a CHD on psychosocial problems and symptoms of posttraumatic stress [70].
- We recommend structural screening through questionnaires for children with DCM on psychosocial problems; mainly on symptoms of anxiety and depression.
- Effective psychosocial interventions for families of children with a CHD need to be developed and should be incorporated in standard clinical practice. Psychoeducational portals offer a promising option but should be further examined.
- Psychoeducation can be sufficient in decreasing symptoms of posttraumatic stress in children and adolescents with subthreshold PTSD after medical trauma.
- EMDR can be beneficial for children with increased symptoms of blood-injection-injury phobia, depression, and sleep problems after a medical trauma.

REFERENCES

1. Barrett P, Fisak B, Cooper M. The treatment of anxiety in young children: Results of an open trial of the Fun FRIENDS program. Behav Change. 2015; 32(4).
2. Carlyle DA. With a little help from FUN FRIENDS young children can overcome anxiety. Community Pract. 2014; 87(8): 26-9.
3. Fisak B, Gallegos-Guajardo J, Verreynne M, Barrett P. The results of a targeted open trial of the Fun FRIENDS combined with a concurrent parent-based intervention. Ment Health Prev. 2018; 10: 35-41.
4. Nilsen TS, Eisemann M, Kvernmo S. Predictors and moderators of outcome in child and adolescent anxiety and depression: a systematic review of psychological treatment studies. Eur Child Adolesc Psychiatry. 2013; 22(2): 69-87.
5. Pahl KM, Barrett PM. The development of social-emotional competence in preschool-aged children: An introduction to the Fun FRIENDS program. J Psychol Couns Sch. 2007; 17(1): 81-90.
6. Karsdorp PA, Everaerd W, Kindt M, Mulder BJ. Psychological and cognitive functioning in children and adolescents with congenital heart disease: a meta-analysis. J Pediatr Psychol. 2007; 32(5): 527-41.
7. McCusker CG, Doherty NN, Molloy B, Rooney N, Mulholland C, Sands A, et al. A randomized controlled trial of interventions to promote adjustment in children with congenital heart disease entering school and their families. J Pediatr Psychol. 2012; 37(10): 1089-103.
8. Wilding S, Conner M, Sandberg T, Prestwich A, Lawton R, Wood C, et al. The question-behaviour effect: A theoretical and methodological review and meta-analysis. Eur Rev Soc Psychol. 2016; 27(1).
9. Arrindell WA. Changes in waiting-list patients over time: data on some commonly-used measures. Beware! Behav Res Ther. 2001; 39(10): 1227-47.
10. Levy RL, van Tilburg MA, Langer SL, Romano JM, Walker LS, Mancl LA, et al. Effects of a Cognitive Behavioral Therapy Intervention Trial to Improve Disease Outcomes in Children with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016; 22(9): 2134-48.
11. Stapersma L, van den Brink G, van der Ende J, Szigethy EM, Beukers R, Korpershoek TA, et al. Effectiveness of Disease-Specific Cognitive Behavioral Therapy on Anxiety, Depression, and Quality of Life in Youth With Inflammatory Bowel Disease: A Randomized Controlled Trial. J Pediatr Psychol. 2018; 43(9): 967-80.
12. Szigethy E, Bujoreanu SI, Youk AO, Weisz J, Benhayon D, Fairclough D, et al. Randomized efficacy trial of two psychotherapies for depression in youth with inflammatory bowel disease. J Am Acad Child Adolesc Psychiatry. 2014; 53(7): 726-35.
13. Bienvenu OJ, Ginsburg GS. Prevention of anxiety disorders. Int Rev Psychiatry. 2007; 19(6): 647-54.
14. Bittner A, Egger HL, Erkanli A, Jane Costello E, Foley DL, Angold A. What do childhood anxiety disorders predict? J Child Psychol Psychiatry. 2007; 48(12): 1174-83.

15. Copeland WE, Shanahan L, Costello J, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. Arch Gen Psychiatry. 2009; 66(7).

16. Open Science Collaboration. Estimating the reproducibility of psychological science. Science. 2015; 349(6251).

17. Hughes B. Psychology in Crisis: Macmillian International Higher Education; 2018.

18. Kuhberger A, Fritz A, Scherndl T. Publication bias in psychology: a diagnosis based on the correlation between effect size and sample size. PLoS One. 2014; 9(9): e105825.

19. Rothstein HR, Sutton AJ, Borenstein M. Publication bias in meta-analysis: Prevention, assessment and adjustments. West Sussex: John Wiley & Sons Ltd; 2005.

20. Law E, Fisher E, Eccleston C, Palermo TM. Psychological interventions for parents of children and adolescents with chronic illness. Cochrane Database Syst Rev. 2019; 3: CD009660.

21. Bellinger DC, Newburger JW, Wypij D, Kuban KC, duPlesssis AJ, Rappaport LA. Behaviour at eight years in children with surgically corrected transposition: The Boston Circulatory Arrest Trial. Cardiol Young. 2009; 19(1): 86-97.

22. McCusker CG, Armstrong MP, Mullen M, Doherty NN, Casey FA. A sibling-controlled, prospective study of outcomes at home and school in children with severe congenital heart disease. Cardiol Young. 2013; 23(4): 507-16.

23. Thompson RJ, Jr., Gustafson KE, Hamlett KW, Spock A. Stress, coping, and family functioning in the psychological adjustment of mothers of children and adolescents with cystic fibrosis. J Pediatr Psychol. 1992; 17(5): 573-85.

24. Brosig CL, Mussatto KA, Kuhn EM, Tweddell JS. Psychosocial outcomes for preschool children and families after surgery for complex congenital heart disease. Pediatr Cardiol. 2007; 28(4): 255-62.

25. Caris EC, Dempster N, Wernovsky G, Miao Y, Moore-Clingenpeel M, Neely T, et al. Perception scores of siblings and parents of children with hypoplastic left heart syndrome. Congenit Heart Dis. 2018; 13(4): 528-32.

26. Kolaitis GA, Meentken MG, Utens E. Mental Health Problems in Parents of Children with Congenital Heart Disease. Front Pediatr. 2017; 5: 102.

27. Sharpe D, Rossiter L. Siblings of children with a chronic illness: a meta-analysis. J Pediatr Psychol. 2002; 27(8): 699-710.

28. Wei H, Roscigno CI, Hanson CC, Swanson KM. Families of children with congenital heart disease: A literature review. Heart Lung. 2015; 44(6): 494-511.

29. Utens E, Callus E, Levert EM, Groote K, Casey F. Multidisciplinary family-centred psychosocial care for patients with CHD: consensus recommendations from the AEPC Psychosocial Working Group. Cardiol Young. 2018; 28(2): 192-8.

30. Law EF, Fisher E, Fales J, Noel M, Eccleston C. Systematic review and meta-analysis of parent and family-based interventions for children and adolescents with chronic medical conditions. J Pediatr Psychol. 2014; 39(8): 866-86.

31. Eccleston C, Fisher E, Law E, Bartlett J, Palermo TM. Psychological interventions for parents of children and adolescents with chronic illness. Cochrane Database Syst Rev. 2015; 4: CD009660.

32. Cassidy AR, Ilardi D, Bowen SR, Hampton LE, Heinrich KP, Loman MM, et al. Congenital heart disease: A primer for the pediatric neuropsychologist. Child Neuropsychol. 2017: 1-44.

33. Etnel JRG, van Dijk APJ, Kluin J, Bertels RA, Utens EMWJ, van Galen E, et al. Development of an Online, Evidence-Based Patient Information Portal for Congenital Heart Disease: A Pilot Study. Front Cardiovasc Med. 2017; 4.

34. Hirshfeld-Becker DR, Biederman J. Rationale and principles for early intervention with young children at risk for anxiety disorders. Clin Child Fam Psychol Rev. 2002; 5(3): 161-72.

35. Essau CA, Lewinsohn PM, Lim JX, Ho MR, Rohde P. Incidence, recurrence and comorbidity of anxiety disorders in four major developmental stages. J Affect Disord. 2018; 228: 248-53.

36. Essau CA, Lewinsohn PM, Olaya B, Seeley JR. Anxiety disorders in adolescents and psychosocial outcomes at age 30. J Affect Disord. 2014; 163: 125-32.

37. Connolly SD, Bernstein GA, Work Group on Quality I. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2007; 46(2): 267-83.

38. Donovan CL, March S. Online CBT for preschool anxiety disorders: a randomised control trial. Behav Res Ther. 2014; 58: 24-35.

39. Fox JK, Warner CM, Lerner AB, Ludwig K, Ryan JL, Colognori D, et al. Preventive intervention for anxious preschoolers and their parents: Strengthening early emotional development. Child Psychiatry Hum Dev. 2012; 43(4).

40. Drotar D. Psychological interventions in childhood chronic illness. Washington DC: American psychological Association; 2006.

41. Stehl ML, Kazak AE, Alderfer MA, Rodriguez A, Hwang WT, Pai AL, et al. Conducting a randomized clinical trial of an psychological intervention for parents/caregivers of children with cancer shortly after diagnosis. J Pediatr Psychol. 2009; 34(8): 803-16.

42. Achenbach TM, Rescorla LA. Manual for the ASEBA school-age forms & profiles. Burlington, Vermont: University of Vermont, Research Center for Children, Youth, & Families; 2001.

43. Wray J, Radley-Smith R. Cognitive and behavioral functioning of children listed for heart and/or lung transplantation. Am J Transplant. 2010; 10(11): 2527-35.

44. Pinquart M, Shen Y. Anxiety in children and adolescents with chronic physical illnesses: a meta-analysis. Acta Paediatr. 2011; 100(8): 1069-76.

45. Pinquart M, Shen Y. Depressive symptoms in children and adolescents with chronic physical illness: an updated meta-analysis. J Pediatr Psychol. 2011; 36(4): 375-84.

46. Hommel KA, Chaney JM, Wagner JL, White MM, Hoff AL, Mullins LL. Anxiety and depression in older adolescents with long-standing asthma: The role of illness uncertainty. Child Health Care. 2003; 32(1): 51-63.

47. Miller JM, Kustra RP, Vuong A, Hammer AE, Messenheimer JA. Depressive symptoms in epilepsy: prevalence, impact, aetiology, biological correlates and effect of treatment with antiepileptic drugs. Drugs. 2008; 68(11): 1493-509.

48. Pinquart M. Do the parent-child relationship and parenting behaviors differ between families with a child with and without chronic illness? A meta-analysis. J Pediatr Psychol. 2013; 38(7): 708-21.

49. Menteer J, Beas VN, Chang JC, Reed K, Gold JI. Mood and health-related quality of life among pediatric patients with heart failure. Pediatr Cardiol. 2013; 34(2): 431-7.

50. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol. 2006; 48(8): 1527-37.

51. Fan H, Yu W, Zhang Q, Cao H, Li J, Wang J, et al. Depression after heart failure and risk of cardiovascular and all-cause mortality: a meta-analysis. Prev Med. 2014; 63: 36-42.

52. Luyster FS, Hughes JW, Gunstad J. Depression and anxiety symptoms are associated with reduced dietary adherence in heart failure patients treated with an implantable cardioverter defibrillator. J Cardiovasc Nurs. 2009; 24(1): 10-7.

53. Weisz JR, Kuppens S, Ng MY, Eckshtain D, Ugueto AM, Vaughn-Coaxum R, et al. What five decades of research tells us about the effects of youth psychological therapy: A multilevel meta-analysis and implications for science and practice. Am Psychol. 2017; 72(2): 79-117.

54. Compton SN, March JS, Brent D, Albano AMt, Weersing R, Curry J. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. J Am Acad Child Adolesc Psychiatry. 2004; 43(8): 930-59.

55. Bae H, Kim D, Park YC. Eye movement desensitization and reprocessing for adolescent depression. Psychiatry Investig. 2008; 5(1): 60-5.

56. De Jongh A, van den Oord HJ, ten Broeke E. Efficacy of eye movement desensitization and reprocessing in the treatment of specific phobias: Four single-case studies on dental phobia. J Clin Psychol. 2002; 58(12): 1489-503.

57. de Roos C, van der Oord S, Zijlstra B, Lucassen S, Perrin S, Emmelkamp P, et al. EMDR versus cognitive behavioral writing therapy versus waitlist in pediatric PTSD following single-incident trauma: A multi-center randomized clinical trial. J Child Psychol Psychiatry. 2017; 58: 1219-28.

58. Doering S, Ohlmeier MC, de Jongh A, Hofmann A, Bisping V. Efficacy of a trauma-focused treatment approach for dental phobia: a randomized clinical trial. Eur J Oral Sci. 2013; 121(6): 584-93.

59. Raboni MR, Alonso FF, Tufik S, Suchecki D. Improvement of mood and sleep alterations in posttraumatic stress disorder patients by eye movement desensitization and reprocessing. Front Behav Neurosci. 2014; 8: 209.

60. Moreno-Alcazar A, Treen D, Valiente-Gomez A, Sio-Eroles A, Perez V, Amann BL, et al. Efficacy of Eye Movement Desensitization and Reprocessing in Children and Adolescent with Post-traumatic Stress Disorder: A Meta-Analysis of Randomized Controlled Trials. Front Psychol. 2017; 8: 1750.

61. Rodenburg R, Benjamin A, de Roos C, Meijer AM, Stams GJ. Efficacy of EMDR in children: a meta-analysis. Clin Psychol Rev. 2009; 29(7): 599-606.

62. Shapiro E. EMDR and early psychological intervention following trauma. Eur Rev Applied Psychol. 2012; 62(4).

63. Parent J, Forehand R, Pomerantz H, Peisch V, Seehuus M. Father Participation in Child Psychopathology Research. J Abnorm Child Psychol. 2017; 45(7): 1259-70.

64. Phares V, Lopez E, Fields S, Kamboukos D, Duhig AM. Are fathers involved in pediatric psychology research and treatment? J Pediatr Psychol. 2005; 30(8): 631-43.

65. De Los Reyes A, Augenstein TM, Wang M, Thomas SA, Drabick DAG, Burgers DE, et al. The validity of the multi-informant approach to assessing child and adolescent mental health. Psychol Bull. 2015; 141(4): 858-900.

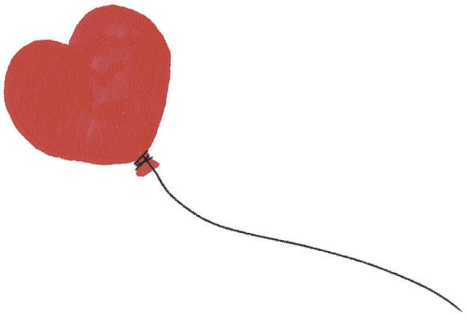
66. van der Ende J, Verhulst FC, Tiemeier H. Agreement of informants on emotional and behavioral problems from childhood to adulthood. Psychol Assess. 2012; 24(2): 293-300.

67. Berkes A, Varni JW, Pataki I, Kardos L, Kemeny C, Mogyorosy G. Measuring health-related quality of life in Hungarian children attending a cardiology clinic with the Pediatric Quality of Life Inventory. Eur J Pediatr. 2010; 169(3): 333-47.

68. Uzark K, Jones K, Slusher J, Limbers CA, Burwinkle TM, Varni JW. Quality of life in children with heart disease as perceived by children and parents. Pediatrics. 2008; 121(5): e1060-7.

69. Wilmot I, Cephus CE, Cassedy A, Kudel I, Marino BS, Jefferies JL. Health-related quality of life in children with heart failure as perceived by children and parents. Cardiol Young. 2016; 26(5): 885-93.

70. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012; 126(9): 1143-72.



8

CHAPTER 8

Summary

Samenvatting

SUMMARY

The main aim of this thesis was to examine and improve the psychosocial well-being of children with congenital or acquired heart disease. The general introduction in **chapter 1** describes the background and main aims of the studies included in this thesis. The umbrella term 'congenital heart defects' (CHDs) describes multiple structural abnormalities of the heart and/or intrathoracic great vessels which emerge before birth. CHDs are the most common birth defect, estimated to affect 8 out of 1,000 live births. Children with a CHD are at elevated risk of emotional and behavioral problems (especially internalizing problems), posttraumatic stress symptoms, social problems, school problems, low exercise levels, and neuropsychological deficits. Moreover, developmental milestones such as starting school are more challenging for children with a CHD and their families than for healthy peers and their families. It is well-known that parental mental health influences children's well-being. Unfortunately, parents of children with a CHD are also more likely to experience mental health problems. Previously, to improve the psychosocial well-being of children with a CHD and their families, the multidisciplinary Congenital Heart Disease Intervention Program (CHIP) - School was developed by Dr. McCusker and colleagues from the Royal Belfast Hospital for Sick Children. CHIP-School targeted to improve the psychosocial well-being of parents of children with a CHD who were entering school, aiming to indirectly improve children's outcomes. Though CHIP-School obtained positive results regarding maternal mental health, perceived strain on the family, and school absence, children's psychosocial well-being did not significantly increase. To improve these results, we extended and innovated the CHIP-School program by also including exercises for young children with CHDs and siblings in the program, thereby creating the CHIP-Family intervention. In this thesis, we investigated whether CHIP-Family improved the psychosocial well-being of young children (4-7 years old) with a CHD and their families.

Furthermore, high levels of posttraumatic stress symptoms and posttraumatic stress disorder (PTSD) have been described in children who were hospitalized or underwent painful medical procedures. In adults, eye movement desensitization and reprocessing (EMDR) has been established as an effective treatment for posttraumatic stress symptoms and PTSD. In children, however, relatively few studies have been conducted into EMDR, but available studies show promising results. However, the trauma types studied were not focused specifically on medically-related trauma, but mainly concerned abuse, violence, or natural

disasters. Therefore, in this thesis we aimed to examine the effectiveness of EMDR in children with a subthreshold PTSD after a medically-related event, including children with a CHD. The focus was on subthreshold PTSD as this is often underestimated, but may result in similar impairments as a clinical diagnosis of PTSD.

Another aim of this thesis was to study emotional and behavioral problems of children with dilated cardiomyopathy (DCM), an acquired heart disease. Cardiomyopathies are disorders of the heart muscle. DCM is the most common type in children, affecting approximately 0.57 to 0.73 per 100,000 children per year. DCM has a poor prognosis and is the leading cause of cardiac transplantation. Research has already shown that children with DCM have lower health-related quality of life (HRQoL) than their healthy peers and that physical HRQoL predicts mortality and cardiac transplantation. However, since little was known about emotional and behavioral problems in pediatric DCM, we performed a study into these problems.

Chapter 2 describes the results of our clinical open trial of the previously developed cognitive behavioral (CBT) Fun FRIENDS program for 4-8-year-old children with an anxiety disorder. We aimed to investigate outcomes of the Fun FRIENDS program for clinically anxious children, but also aimed to investigate its outcomes since several exercises of the Fun FRIENDS program were implemented in the CHIP-Family intervention for young children with CHDs and their siblings. In our open trial, we investigated whether emotional and behavioral problems of 28 young children (4-8 years old) with anxiety disorders decreased after completing the CBT Fun FRIENDS program. Fun FRIENDS comprises 12 weekly group sessions (1.5 hour each) which were provided to groups of 3 to 5 children. From pre-intervention to direct post-intervention, parents' reports on the Child Behavior Checklist (CBCL) significantly decreased as to overall emotional and behavioral problems, internalizing problems, and on the DSM-scale anxiety problems, whereas scores on the empirical anxious/depressed problems scale and externalizing problems did not decrease. Assessments using the Anxiety Disorders Interview Schedule for Children (ADIS-C) showed that the mean number of anxiety disorders and level of symptom interference significantly decreased. Our results are largely in line with previous positive findings regarding the Fun FRIENDS program. However, in 8 to 12-year-old children, previous trials have found that the FRIENDS for Life program, on which Fun FRIENDS was based, also elicited positive results as to depressive problems. Presumably, depressive and externalizing problems did not significantly

decrease in children in our trial, because these children did not have high levels of depressive or externalizing problems at baseline.

Chapter 3 describes the study protocol of a randomized controlled trial (RCT) to test the effectiveness of the multidisciplinary psychosocial CHIP-Family program for young children with a CHD and their families. Ninety-three families were randomized into care as usual (CAU; medical care "only") or CAU plus CHIP-Family. CHIP-Family consisted of a parent module and a child module. The parent module consisted of a 6-hour group workshop and an individual 4-week follow-up session. In the group workshop, two psychologists provided psychoeducation and discussed and practiced problem prevention techniques and parenting skills. A pediatric cardiologist addressed medical and psychosocial issues in the presence of a psychologist. In the follow-up session, individual parent couples discussed the problem prevention home exercise, remaining questions, and future coping strategies with two psychologists. The child module consisted of a 6-hour group workshop in which children with a CHD participated with a sibling or friend. Two psychologists taught the children CBT techniques through exercises from the Fun FRIENDS protocol (e.g., helpful thoughts, relaxation techniques, coping with emotions). Also, the children did sports exercises with a pediatric physiotherapist in the presence of their parents. Outcomes were completed at baseline and 6-month follow-up by parents, teachers, and the child itself. Primary outcomes were children's emotional and behavioral problems and parental mental health. Secondary outcomes concerned family functioning, children's school functioning, sports enjoyment, and quality of life, and parents' worry, disease-specific knowledge, quality of life, and program satisfaction.

In **chapter 4**, we presented the results of our RCT into the effectiveness of CHIP-Family (CHIP-Family group: N=49 vs. CAU group: N=44). Though parents evaluated CHIP-Family positively (mean ratings 7.4-8.1 on a 10-point scale), compared to CAU, the CHIP-Family program did not elicit significant improvements on the aforementioned outcomes. However, in both the CAU and the CHIP-Family group, fathers and mothers reported significant decreases as to children's emotional and behavioral problems. These decreases may be explained by parents' heightened awareness of emotional and behavioral problems induced by merely participating in the study. Overall, CHIP-Family generated less favorable results than the previously developed CHIP-School. This may be due to differences in the protocols and timing of the interventions. CHIP-School included a bicycle exercise stress test to challenge parents' assumptions regarding their child's fragility, whereas, for

logistical reasons, in our CHIP-Family study it was not possible to include a bicycle exercise stress test. Furthermore, including the child module may have diminished the importance as perceived by parents of the CHIP-Family parent program. Finally, in CHIP-Family, some children were already attending school, whereas in CHIP-School children were all in the developmental transition of starting school.

In **chapter 5**, we described the results of our study into the level of emotional and behavioral problems in children with DCM (N=68, 1.5-18 years old). We also examined whether depressive and anxiety symptoms corrected for heart failure severity predicted death or cardiac transplantation. Compared to normative data, a significantly larger proportion of young children (i.e., 1.5-5-year-olds) with DCM experienced a clinical or borderline level of somatic complaints (24.3% vs. 8.0%), whereas a significantly smaller proportion showed externalizing problems (5.4% vs. 17.0%). As to older children with DCM (i.e., 6-18-year-olds), compared to normative data, a larger proportion showed internalizing problems (38.7% vs. 17.0%), including somatic, depressive, and anxiety problems. The two previous small studies showed inconsistent results. The first study found that 50% (N=6 out of 12) of children with cardiomyopathy who were listed for cardiac transplantation experienced clinical levels of emotional and behavioral problems. The second study, however, specifically examined depressive problems in pediatric DCM (N=15) and did not find an elevated level of symptoms. Furthermore, our results showed that the risk of death or cardiac transplantation was not predicted by anxiety or depressive problems, but was positively associated with heart failure severity. In adult heart failure populations, the association between anxiety and depressive problems and adverse clinical outcomes is well-established. An explanation for the discrepancy with our findings concerning the predictive value of anxiety/depressive problems may be that, in children, parents may function as a buffer by compensating for anxious/depressed children's diminished self-care.

Chapter 6 presents the short-term results of our RCT examining the effectiveness of EMDR in children with medically-related subthreshold PTSD. After screening 399 children, we randomized 74 children (4-15 years old) who had subthreshold PTSD following at least one hospitalization into CAU (N=37; medical care "only") or EMDR treatment (N=37). To measure symptoms of posttraumatic stress, anxiety, depression, and sleep problems, parents and children completed questionnaires at baseline and approximately 10 weeks after the start of EMDR or CAU. Children in both the CAU and the EMDR group improved significantly on all outcomes. Remarkably, EMDR was not superior in improving posttraumatic stress symptoms.

However, children in the EMDR group did show significantly larger improvements regarding blood-injection-injury phobia and depression (child-report), and children's sleep problems (parent-report and child-report). Our results suggest that receiving psychoeducation from a mental health care professional and screening for psychological problems may be sufficient to decrease PTSD symptoms in children with subthreshold PTSD.

Finally, in **chapter 7** we provide a general discussion in which we summarized and discussed the main findings of this manuscript (see above) and provided recommendations for future research and clinical practice. To improve psychosocial interventions for children with heart defects, the target group, content, mode of delivery, and timing should be considered. Regarding the *target group*, it is widely established that such an intervention should be family-focused. However, our results indicate that directly including young children in an intervention may not necessarily improve the effectiveness of an intervention. Regarding the *content of the intervention*, CBT and problem prevention therapy have shown most beneficial results. As the difficulties experienced by children with a CHD encompass a broad medical and psychosocial range, involving professionals from multiple disciplines is valuable. In our CHIP-Family study, the psychosocial and medical topics discussed by a pediatric cardiologist and discussing such topics with other families were considered most useful. However, in the CHIP-School study, the bicycle exercise stress test was rated as the most helpful component. Moreover, to further improve children's outcomes, an intervention with multiple sessions may be needed. Now, the CBT exercises were combined into one 4-hour session. Regarding the *mode of delivery*, as mentioned, the group format was highly appreciated by parents. Perhaps a larger group format as used in CHIP-School optimizes the support impact, whereas it may decrease levels of personal attention. An online evidence-based patient information portal might offer sufficient support for children with subclinical psychological symptoms. Regarding the *timing* of a psychosocial intervention, early intervention in children has a number of benefits. Early intervention may prevent disorders from becoming chronic and through early intervention effects may be optimized as problems are less engrained and neuroplasticity is higher. However, CHIP-School may have obtained more positive results than CHIP-Family because the intervention was timed more specifically at a developmental transition. As to EMDR, our results suggested that decreases in depressive and sleep problems were larger if more time had elapsed since the last medical event.

The studies described in this thesis add to the limited body of knowledge as to psychosocial interventions for children with heart defects. For both the CHIP-Family and EMDR intervention, treatment integrity and parents' satisfaction ratings were high. Furthermore, our study examining the effectiveness of CHIP-Family was the first to examine a psychosocial intervention with a specific module for children with a CHD. The EMDR study was the first study that investigated EMDR in children with medically-related subthreshold PTSD. Moreover, in the CHIP-Family, EMDR, and the DCM studies, we recruited participants from multiple centers across the Netherlands, which improves generalizability of our findings. Another strength is that, considering prevalence rates and previous research, our studies into EMDR and DCM used substantial sample sizes.

A future RCT is needed to determine the effectiveness of Fun FRIENDS in treating anxiety disorders. As to children with heart defects, future research should invest in developing and testing effective psychosocial interventions. The added value of a specific child module also remains to be examined. Furthermore, it would be valuable to investigate which children and families benefit sufficiently from psychoeducation alone. Regarding EMDR, the best timing to provide treatment for children should be studied. As to pediatric DCM, many psychosocial aspects remain to be examined. Future research should investigate children's self-reports of emotional and behavioral problems, the association between disease severity and the level of emotional and behavioral problems, examine age differences in more detail, and perform qualitative analyses. At the end of chapter 7, a description of implications and recommendations for clinical practice is provided.

SAMENVATTING

Het doel van dit proefschrift was om het psychosociale welzijn van kinderen met een aangeboren of verworven hartziekte te onderzoeken en te verbeteren. De algemene inleiding in **hoofdstuk 1** beschrijft de achtergrond en hoofddoelen van de studies die opgenomen zijn in dit proefschrift. 'Aangeboren hartafwijking' (AHA) is een overkoepelende term die verschillende afwijkingen beschrijft in de bouw van het hart en/of de grote intrathoracale bloedvaten. AHA's ontstaan per definitie voor de geboorte. AHA's zijn de meest voorkomende aangeboren afwijking: naar schatting 8 van de 1.000 levendgeborenen hebben een AHA. Kinderen met een AHA hebben een verhoogd risico op emotionele en gedragsproblemen (met name internaliserende problemen), posttraumatische stresssymptomen, sociale problemen, schoolproblemen, verminderde fysieke activiteit en neuropsychologische problemen. Bovendien bieden mijlpalen zoals het starten van school grotere uitdagingen voor kinderen met een AHA en hun gezin dan voor gezonde leeftijdsgenoten en hun gezin. We weten hiernaast dat de mentale gezondheid van ouders invloed heeft op het welzijn van hun kinderen. Ouders van kinderen met een AHA hebben zelf ook meer kans op psychische problemen. Voorheen is, om het psychosociale welzijn van kinderen met een AHA en hun gezin te verbeteren, het multidisciplinaire *Congenital Heart Disease Intervention Program* (CHIP) - School ontwikkeld door prof. dr. McCusker en zijn collega's van het Royal Belfast Hospital of Sick Children in Ierland. De CHIP-School interventie had als doel het psychosociale welzijn te verbeteren van ouders van kinderen met een AHA die voor het eerst naar school gingen, en beoogde indirect het welzijn van de kinderen te verbeteren. Hoewel CHIP-School positieve resultaten behaalde met betrekking tot de mentale gezondheid van moeders, belasting van het gezin en schoolabsentie, nam het psychosociale welzijn van de kinderen niet significant toe. Om deze resultaten te verbeteren, hebben we het CHIP-School programma uitgebreid door een module met oefeningen voor jonge kinderen met een AHA en hun broers en zussen in het programma op te nemen. Deze vernieuwde interventie heet "CHIP-Familie". Vervolgens hebben we, zoals beschreven in dit proefschrift, onderzocht of deelname aan CHIP-Familie het psychosociale welzijn van jonge kinderen (4-7 jaar oud) met een AHA en hun families verbeterde.

Daarnaast zijn verhoogde niveaus van posttraumatische stresssymptomen en posttraumatische stressstoornis (PTSS) beschreven bij kinderen die een ziekenhuisopname of medische procedures hebben ondergaan. Bij volwassenen is de effectiviteit van *eye movement desensitization and reprocessing* (EMDR) in

het behandelen van posttraumatische stresssymptomen en PTSS al aangetoond. Bij kinderen zijn er nog relatief weinig studies gedaan naar EMDR, maar de resultaten van de beschikbare studies zijn veelbelovend. De in eerdere studies onderzochte trauma's waren echter anders van aard (met name geweld, misbruik, of natuurrampen) en niet medisch gerelateerd. Daarom was een doel van dit proefschrift om de effectiviteit van EMDR bij kinderen met subklinische PTSS na een medisch gerelateerd trauma te onderzoeken. Een deel van de deelnemers aan dit onderzoek betrof kinderen met een AHA. De nadruk lag op subklinische PTSS, omdat subklinische PTSS vaak wordt onderschat, maar kan leiden tot vergelijkbare beperkingen als een klinische PTSS.

Een ander doel van dit proefschrift was het bestuderen van emotionele en gedragsproblemen van kinderen met gedilateerde cardiomyopathie (DCM). Cardiomyopathie is een aandoening van de hartspier. DCM is het meest voorkomende type bij kinderen en treft ongeveer 0,57 tot 0,73 per 100.000 kinderen per jaar. DCM heeft over het algemeen een slechte prognose en is de meest voorkomende reden voor een harttransplantatie. Eerder onderzoek heeft al aangetoond dat kinderen met DCM een lagere gezondheidsgerelateerde kwaliteit van leven (GKvL) hebben dan hun gezonde leeftijdsgenoten en dat fysieke GKvL mortaliteit en harttransplantatie voorspelt. Omdat er echter weinig onderzoek gedaan is naar emotionele en gedragsproblemen bij kinderen met DCM, hebben wij onderzoek gedaan naar deze problemen en de resultaten in dit proefschrift beschreven.

Hoofdstuk 2 beschrijft de resultaten van onze klinische open trial van het eerder ontwikkelde cognitief gedragstherapeutische (CGT) Fijn VRIENDEN-programma voor kinderen van 4-8 jaar met een angststoornis. We wilden de resultaten na het volgen van het Fijn VRIENDEN-programma onderzoeken bij kinderen met een angststoornis. Daarnaast waren wij in de resultaten van het Fijn VRIENDEN-programma geïnteresseerd, omdat verschillende oefeningen van het Fijn VRIENDEN-programma werden opgenomen in de CHIP-Familie interventie voor jonge kinderen met een AHA en hun broertjes en zusjes. In onze open trial onderzochten we of emotionele en gedragsproblemen van 28 jonge kinderen (4-8 jaar oud) met angststoornissen afnamen na het voltooien van het CGT Fijn VRIENDEN-programma. Dit programma bestaat uit 12 wekelijkse 1,5 uur durende groepssessies die gegeven werden aan groepen van 3 tot 5 kinderen. Van pre-interventie tot directe post-interventie lieten ouderrapportages op de Child Behavior Checklist (CBCL) significante verminderingen zien met betrekking

tot algehele emotionele en gedragsproblemen, internaliserende problemen en de score op de DSM-schaal angstproblemen, terwijl de scores op de empirische schaal angstig/depressieve problemen en externaliserende problemen niet significant verminderden. Bovendien nam het gemiddelde aantal angststoornissen en de symptoominterferentie aanzienlijk af, zoals bepaald met het Anxiety Disorders Interview Schedule for Children (ADIS-C). Onze resultaten zijn grotendeels in lijn met eerdere bevindingen betreffende het Fijn VRIENDEN programma. Uit eerdere onderzoeken met kinderen van 8-12 jaar is echter gebleken dat het VRIENDEN voor het Leven-programma, waarop Fijn VRIENDEN is gebaseerd, positieve resultaten behaalde met betrekking tot depressieve problemen. Vermoedelijk namen depressieve en externaliserende problemen niet significant af in onze studie omdat onze deelnemers geen hoge niveaus van depressieve of externaliserende problemen hadden voorafgaand aan de interventie.

Hoofdstuk 3 beschrijft het studieprotocol van ons gerandomiseerd gecontroleerd onderzoek (RCT) naar de effectiviteit van het multidisciplinaire psychosociale CHIP-Familie programma voor jonge kinderen met een AHA en hun gezin. Drieënnegentig gezinnen werden gerandomiseerd in de controlegroep (“alleen” medische zorg) of in de CHIP-Familie groep. CHIP-Familie bestond uit een oudermodule en een kindermodule. De oudermodule bestond uit een groepsworkshop van 6 uur en een individuele vervolgsessie één maand na de workshop. In de groepsworkshop gaven twee psychologen voor psycho-educatie en bespraken en oefenden ze probleempreventietechnieken en opvoedvaardigheden. Een kindercardioloog besprak in bijzijn van een psycholoog medische en psychosociale kwesties. In de vervolgsessie bespraken ouderparen de probleempreventie thuisopdracht, resterende vragen en toekomstige copingstrategieën met twee psychologen. De kindermodule bestond uit een 6 uur durende groepsworkshop waaraan kinderen met een AHA deelnamen met een broer of zus of vriend(in). Twee psychologen leerden de kinderen CGT-technieken aan door middel van oefeningen uit het Fijn VRIENDEN protocol (bijvoorbeeld helpende gedachten, ontspanning, omgaan met emoties). Ook deden de kinderen in de aanwezigheid van hun ouders sportoefeningen met een kinderfysiotherapeut. Bij baseline en na 6 maanden werden vragenlijsten ingevuld door ouders, leerkrachten en de kinderen zelf. Primaire uitkomstmaten waren de emotionele en gedragsproblemen van kinderen en de mentale gezondheid van de ouders. Secundaire uitkomstmaten hadden betrekking op het functioneren van het gezin, functioneren op school, plezier in sport en kwaliteit van leven van het kind, ouderlijke zorgen, ziekte specifieke kennis, kwaliteit van leven van het ouders en tevredenheid over het programma.

In **hoofdstuk 4** worden de resultaten gepresenteerd van onze RCT naar de effectiviteit van CHIP-Familie (CHIP-Familie groep: N=49 versus controlegroep: N=44). Hoewel deelnemende ouders CHIP-Familie positief beoordeelden (gemiddelde beoordelingen 7,4 tot 8,1 op een 10-puntsschaal), leverde het programma vergeleken met de gebruikelijke zorg geen significante verbeteringen op bovengenoemde uitkomstmaten. Echter, in zowel de controle- als de CHIP-Familie groep rapporteerden vaders en moeders een significante vermindering in emotionele en gedragsproblemen van hun kinderen. Deze vermindering kan mogelijk worden verklaard vanuit ouders' verhoogde bewustwording van emotionele en gedragsproblemen door deelname aan het onderzoek. Over het algemeen werden met CHIP-Familie minder positieve resultaten behaald dan met het eerder onderzochte CHIP-School programma. Dit kan verklaard worden vanuit verschillen in de protocollen en timing van de interventies. In CHIP-School was onder andere uit een fietstest voor kinderen opgenomen om overtuigingen van ouders met betrekking tot de kwetsbaarheid van hun kind op de proef te stellen. De fietsproef kon om logistieke redenen niet worden opgenomen in het protocol van CHIP-Familie. Ook kan het toevoegen van een specifieke kindermodule het belang dat ouders zagen ten aanzien van de oudermodule hebben overschaduwd. Ten slotte ging een aantal kinderen die meededen aan het CHIP-Familie onderzoek ten tijde van het aanbieden van de interventie al naar school, terwijl alle kinderen in eerdere CHIP-School programma nog met school moesten starten.

In **hoofdstuk 5** beschrijven we de resultaten van ons onderzoek naar het niveau van emotionele en gedragsproblemen bij kinderen met DCM (N=68, 1,5-18 jaar oud). Ook onderzochten we of depressieve en angstsymptomen, gecorrigeerd voor ernst van hartfalen, overlijden of harttransplantatie voorspelden. Vergeleken met normatieve data ondervond een significant groter deel van de jonge kinderen met DCM (d.w.z. 1,5- tot en met 5-jarigen) een klinisch of borderline niveau aan somatische klachten (24,3% versus 8,0%), terwijl een aanzienlijk kleiner deel externaliserende problemen vertoonde (5,4% versus 17,0%). Vergeleken met normatieve data vertoonde een significant groter deel van de oudere kinderen met DCM (d.w.z. 6- tot en met 18-jarigen) internaliserende problemen (38,7% versus 17,0%), waaronder somatische, depressieve en angstproblemen.

De twee kleine eerder gepubliceerde studies vonden tegenstrijdige resultaten. De eerste studie toonde aan dat 50% (N=6 van de 12) van de kinderen met cardiomyopathie die op de wachtlijst stonden voor een harttransplantatie een klinisch niveau van emotionele en gedragsproblemen vertoonde. De tweede

studie, daarentegen, onderzocht specifiek het niveau van depressieve problemen in kinderen met DCM (N=15) en vond geen verhoogde klachten. Hiernaast vonden we in onze studie dat het risico op mortaliteit en harttransplantatie niet voorspeld werd door angst of depressieve problemen, maar wel positief geassocieerd was met de ernst hartfalen. In populaties van volwassenen met hartfalen is het verband tussen angst- en depressieve problemen en ongunstige klinische resultaten goed vastgesteld. Een verklaring voor het verschil met onze resultaten wat betreft de voorspellende waarde van angst- en depressieve problemen kan zijn dat ouders bij kinderen kunnen fungeren als een buffer door te compenseren voor de verminderde zelfzorg van kinderen met angstige en depressieve klachten.

In **hoofdstuk 6** werden de korte termijn resultaten besproken van onze RCT naar de effectiviteit van EMDR bij kinderen met medisch gerelateerde subklinische PTSS. Na het screenen van 399 kinderen randomiseerden we 74 kinderen (4-15 jaar oud) met subklinische PTSS na minimaal één ziekenhuisopname in een controlegroep (N=37; "alleen" medische zorg) of EMDR-behandeling (N=37). Om symptomen van posttraumatische stress, angst, depressie en slaapproblemen te meten, vulden ouders en kinderen vragenlijsten in bij baseline en ongeveer 10 weken na de start van de EMDR. Kinderen in zowel de controle- als de EMDR-groep gingen significant vooruit op alle uitkomstmaten. Kinderen in de EMDR-groep vertoonden echter significant grotere vooruitgang met betrekking tot bloed-injectie-letselfobie en depressie (gerapporteerd door kinderen) en met betrekking tot slaapproblemen (gerapporteerd door kinderen en ouders). Mogelijk kan psycho-educatie voldoende zijn om PTSS-symptomen te verminderen bij kinderen met subklinische PTSS.

In de algemene discussie in **hoofdstuk 7** hebben we de belangrijkste bevindingen van dit proefschrift samengevat en besproken en hebben we aanbevelingen gedaan voor toekomstig onderzoek en de klinische praktijk. Om psychosociale interventies voor kinderen met hartafwijkingen te verbeteren, moet rekening worden gehouden met de doelgroep, inhoud, wijze van aanbieden en timing. Met betrekking tot de *doelgroep* is algemeen bekend dat een dergelijke interventie gezinsgericht moet zijn. Onze resultaten geven echter aan dat het rechtstreeks betrekken van jonge kinderen bij een interventie niet noodzakelijkerwijs de effectiviteit van een interventie verbetert. Wat betreft de *inhoud* van de interventie, hebben CGT en probleempreventietherapie de meest positieve resultaten laten zien. Omdat de problemen die kinderen met een AHA ondervinden een breed scala van medische en psychosociale kwesties omvatten, is het nuttig om professionals uit meerdere disciplines te betrekken. In onze CHIP-Familie studie werden de psychosociale en

medische onderwerpen besproken door een kindercardioloog en het bespreken van dergelijke onderwerpen met andere families het nuttigst geacht. In het CHIP-School-onderzoek werd de fietsstresstest echter als het nuttigste onderdeel beoordeeld. Bovendien kan een interventie met meerdere sessies nodig zijn om de resultaten van de kinderen verder te verbeteren. Nu waren de CGT oefeningen immers samengevoegd in één korte sessie (4 uur). Wat betreft *het format* waarin de interventie wordt aangeboden werd het groepsformat zeer op prijs gesteld door ouders. Mogelijk zorgt een grotere groep, zoals in CHIP-School gebruikt werd, voor meer ondersteunende impact, terwijl dit ook de persoonlijke aandacht kan verminderen. Een online evidence-based patiënteninformatieportaal biedt mogelijk voldoende ondersteuning voor kinderen en tieners met subklinische psychologische symptomen. Wat de *timing* van een psychosociale interventie betreft, heeft vroege interventie bij kinderen een aantal voordelen. Vroege interventie kan voorkomen dat aandoeningen chronisch worden en door vroege interventie kunnen de effecten worden geoptimaliseerd, omdat problemen minder diepgeworteld zijn en de neuroplasticiteit hoger is. CHIP-School heeft echter mogelijk meer positieve resultaten behaald dan CHIP-Family doordat de interventie meer specifiek was gepland voor een ontwikkelingstransitie. Wat EMDR betreft, suggereerden onze resultaten dat de afname van depressieve en slaapproblemen groter was als er meer tijd was verstreken sinds de laatste medische gebeurtenis.

De studies beschreven in dit proefschrift dragen bij aan de beperkte kennis die nu beschikbaar is wat betreft psychosociale interventies voor kinderen met hartafwijkingen. Van zowel de CHIP-Familie als de EMDR-interventie waren de behandelintegriteit en de tevredenheid van ouders hoog. Bovendien was ons onderzoek naar de effectiviteit van CHIP-Familie het eerste onderzoek dat een psychosociale interventie onderzocht met een specifieke module voor kinderen met een AHA. De EMDR-studie was de eerste studie die EMDR onderzocht bij kinderen met medisch gerelateerde subklinische PTSS. Bovendien hebben we in de CHIP-Familie, EMDR en de DCM-onderzoeken deelnemers uit meerdere centra vanuit heel Nederland geworven, wat de generaliseerbaarheid van onze bevindingen ten goede komt. Een ander sterk punt is dat, gezien de prevalentie van DCM en vergeleken met eerder onderzoek, onze onderzoeken naar EMDR en DCM substantiële steekproefgroottes gebruikten.

In de toekomst is een RCT nodig om de effectiviteit van Fun FRIENDS te kunnen bepalen bij de behandeling van angststoornissen. Wat betreft kinderen met hartafwijkingen, zou toekomstig onderzoek moeten investeren in het ontwikkelen en testen van effectieve psychosociale interventies. De toegevoegde waarde van een specifieke kindermodule moet ook nog worden onderzocht. Verder zou het waardevol zijn om te onderzoeken welke kinderen en gezinnen voldoende baat hebben bij alleen psycho-educatie. Met betrekking tot EMDR moet de beste timing voor de behandeling van kinderen nader worden bestudeerd. Wat DCM bij kinderen betreft, moeten nog veel psychosociale aspecten worden onderzocht. Toekomstig onderzoek moet zelfrapportage van kinderen met betrekking tot emotionele en gedragsproblemen, het verband tussen de ernst van de ziekte en het niveau van emotionele en gedragsproblemen en leeftijdsverschillen in meer detail onderzoeken en kwalitatieve analyses uitvoeren. Aanbevelingen voor de klinische praktijk worden gegeven aan het einde van hoofdstuk 7.

APPENDICES

AUTHOR AFFILIATIONS

Ad J.J.C. Bogers	Department of Thoracic Surgery, Erasmus MC
Anne Zirar	Department of Child and Adolescent Psychiatry/ Psychology, Psychosocial Care Unit, Erasmus MC – Sophia Children's Hospital
Arend D.J. ten Harkel	Department of Pediatrics, division of Pediatric Cardiology, Leiden UMC
Christopher G. McCusker	School of Applied Psychology, University College Cork
Dayenne J. Schreutelkamp	Department of Pediatric Intensive Care, Erasmus MC – Sophia Children's Hospital
Elisabeth M.W.J. Utens	Department of Child and Adolescent Psychiatry/ Psychology, Erasmus MC – Sophia Children's Hospital | Research Institute of Child Development and Education, University of Amsterdam | Academic Center for Child and Adolescent Psychiatry the Bascule, Department of Child and Adolescent Psychiatry, Amsterdam UMC (location AMC)
Elisabeth W.C. Aendekerk	Department of Child and Adolescent Psychiatry/ Psychology, Psychosocial Care Unit, Erasmus MC – Sophia Children's Hospital
Eugène van Galen	Dutch Patient Association for Congenital Heart Disease
Frank A. Casey	Department of Pediatric Cardiology, Royal Belfast Hospital for Sick Children
Gideon J. du Marchie Sarvaas	Department of Pediatrics, division of Pediatric Cardiology, Beatrix Children's Hospital, UMC Groningen
Gwendolyn C. Dieleman	Department of Child and Adolescent Psychiatry/ Psychology, Erasmus MC – Sophia Children's Hospital
Henriëtte A. Moll	Department of Pediatrics, division of Pediatrics, Erasmus MC – Sophia Children's Hospital
Ingrid M. van Beynum	Department of Pediatrics, division of Cardiology, Erasmus MC – Sophia Children's Hospital

Jan van der Ende	Department of Child and Adolescent Psychiatry/ Psychology, Erasmus MC – Sophia Children's Hospital
Jeroen S. Legerstee	Department of Child and Adolescent Psychiatry/ Psychology, Erasmus MC – Sophia Children's Hospital
Johannes M.P.J. Breur	Department of Pediatrics, division of Pediatric Cardiology, Wilhelmina Children's Hospital, UMC Utrecht
Jorieke Duvekot	Department of Child and Adolescent Psychiatry/ Psychology, Psychosocial Care Unit, Erasmus MC – Sophia Children's Hospital
Karolijn Dulfer	Department of Child and Adolescent Psychiatry/ Psychology, Erasmus MC – Sophia Children's Hospital
Lisette E. Rots	Department of Child and Adolescent Psychiatry/ Psychology, Psychosocial Care Unit, Erasmus MC – Sophia Children's Hospital
Lukas A.J. Rammeloo	Department of Pediatrics, division of Pediatric Cardiology, Amsterdam UMC (location VUmc)
Manon H.J. Hillegers	Department of Child and Adolescent Psychiatry/ Psychology, Erasmus MC – Sophia Children's Hospital
Marijke H. van der Meulen	Department of Pediatrics, division of Cardiology, Erasmus MC – Sophia Children's Hospital
Maya G. Meentken	Department of Child and Adolescent Psychiatry/ Psychology, Erasmus MC – Sophia Children's Hospital
Michiel Dalinghaus	Department of Pediatrics, division of Cardiology, Erasmus MC – Sophia Children's Hospital
Nico A. Blom	Department of Pediatrics, division of Pediatric Cardiology, Amsterdam UMC (location AMC), Emma Children's Hospital
Pieter F.A. de Nijs	Department of Child and Adolescent Psychiatry/ Psychology, Erasmus MC – Sophia Children's Hospital
Ramón J.L. Lindauer	Academic Center for Child and Adolescent Psychiatry the Bascule, Department of Child and Adolescent Psychiatry, Amsterdam UMC (location AMC)

Riwka del Canho	Department of Pediatrics, Maasstad Hospital
Ronald B. Tanke	Department of Pediatrics, division of Pediatric Cardiology, Radboud UMC
Susanna L. den Boer	Department of Pediatrics, division of Cardiology, Erasmus MC – Sophia Children's Hospital
Tabitha P.L. van den Adel	Department of Pediatric Physiotherapy, Erasmus MC – Sophia Children's Hospital
Willem A. Helbing	Department of Pediatrics, division of Cardiology, Erasmus MC – Sophia Children's Hospital

PUBLICATIONS

M. van der Mheen, L.M. ter Mors, M.A. van den Hout & D.C. Cath (2018). Routine outcome monitoring bij de behandeling van angststoornissen: diagnosespecifieke versus generieke meetinstrumenten. Tijdschrift voor Psychiatrie, 60 (1), 11-19.

M. van der Mheen, I.M. van Beynum, K. Dulfer, J. van der Ende, E. van Galen, J. Duvekot, L.E. Rots, T.P.L. van den Adel, A.J.J.C. Bogers, C.G. McCusker, F.A. Casey, W.A. Helbing & E.M.W.J. Utens (2018). The CHIP-Family study to improve the psychosocial wellbeing of young children with congenital heart disease and their families: design of a randomized controlled trial. BMC Pediatrics, 18 (230), doi. org/10.1186/s12887-018-1183-y.

E.M.W.J. Utens, L. Stapersma, **M. van der Mheen**, M. van Dalen & A. Dessens (2019). Depressie en angst bij kinderen en jongeren met een lichamelijke aandoening: screening en behandeling. Tijdschrift voor Kinder- en Jeugdpsychotherapie, 46 (1), 108-127.

M. van der Mheen, M.G. Meentken, I.M. van Beynum, J. van der Ende, E. van Galen, A. Zirar, E.W.C. Aendekerk, T.P.L. van den Adel, A.J.J.C. Bogers, C.G. McCusker, M.H.J. Hillegers, W.A. Helbing & E.M.W.J. Utens (2019). CHIP-Family intervention to improve the psychosocial well-being of young children with congenital heart disease and their families: results of a randomised controlled trial. Cardiology in the Young, 29 (7).

M. van der Mheen, M.H. van der Meulen, S.L. den Boer, D.J. Schreutelkamp, J. van der Ende, P.F.A. de Nijs, J.M.P.J. Breur, R.B. Tanke, N.A. Blom, L.A.J. Rammeloo, A.D.J. ten Harkel, G.J. du Marchie Sarvaas, E.M.W.J. Utens* & M. Dalinghaus* (2019). Emotional and behavioral problems in children with dilated cardiomyopathy. European Journal of Cardiovascular Nursing.

M. van der Mheen, J.S. Legerstee, G.C. Dieleman, M.H.J. Hillegers & E.M.W.J. Utens (2019). Cognitive behavioral therapy for anxiety disorders in young children: a Dutch open trial of the Fun FRIENDS program. Behaviour Change.

M.G. Meentken, **M. van der Mheen**, I.M. van Beynum, E.W.C. Aendekerk, J.S. Legerstee, J. van der Ende, R. del Canho, R.J.L. Lindauer, M.H.J. Hillegers, H.A. Moll, W.A. Helbing & E.M.W.J. Utens (2020). EMDR for children with medically

related subthreshold PTSD: Short-term effects on PTSD, blood-injection-injury phobia, depression and sleep. European Journal of Psychotraumatology, 11 (1).

M.G. Meentken, **M. van der Mheen**, I.M. van Beynum, E.W.C. Aendekerk, J.S. Legerstee, J. van der Ende, R. del Canho, R.J.L. Lindauer, M.H.J. Hillegers, W.A. Helbing, H.A. Moll & E.M.W.J. Utens (2019). Long-term effectiveness of EMDR in children and adolescents with medically related subthreshold PTSD – a randomized controlled trial. Submitted.

M. van der Mheen & E.M.W.J. Utens (2020). Psychosocial interventions in families with a child with congenital heart disease. The Journal of Pediatrics, in press.

* These authors share senior authorship.

CURRICULUM VITAE

Malindi van der Mheen was born on September 4th, 1991 in Almelo, the Netherlands, as daughter of Henk and Jennie. With her sisters Mirjam and Yvette, she grew up in Harare (Zimbabwe), Deventer, and Bunnik (the Netherlands). In 2009, she completed her secondary education (gymnasium) at St. Bonifatiuscollege in Utrecht. After a gap year, she went on to study Psychology at Utrecht University, specializing in Clinical Psychology. During her bachelor's program, she also studied at the University of Alberta in Edmonton (Canada) and successfully completed the Von Humboldt honors program. In 2013, she started her master Clinical and Health Psychology at Utrecht University. During this master's program, she completed a clinical internship at the department of Medical Psychology and Social Work of the Wilhelmina Children's Hospital, University Medical Center (UMC) Utrecht. After graduating cum laude (i.e., with distinction) in 2014, she worked on multiple clinical and research projects in the Netherlands and Stellenbosch (South Africa). In 2016, she started her PhD project at the department of Child and Adolescent Psychiatry/ Psychology of the Erasmus MC – Sophia Children's Hospital in Rotterdam, which has resulted in the work described in this thesis. Her project was supervised by prof. dr. E.M.W.J. Utens, dr. I.M. van Beynum and, from 2017 onwards, by prof. dr. M.H.J. Hillegers. Whilst completing her PhD thesis, in September 2018, she started working on several research projects at De Bascule, Academic Centre for Child and Adolescent Psychiatry and Amsterdam UMC. Since November 2019, she works as a postdoctoral researcher at the department of Child and Adolescent Psychiatry of the Amsterdam UMC. Malindi currently lives in Culemborg with Abe.

Malindi van der Mheen, de tweede dochter van Henk en Jennie, werd geboren op 4 september 1991 in Almelo. Met haar zussen Mirjam en Yvette groeide ze op in Harare (Zimbabwe), Deventer en Bunnik. In 2009 behaalde ze haar gymnasiumdiploma aan het St. Bonifatiuscollege te Utrecht. Na een tussenjaar ging ze psychologie studeren aan de Universiteit Utrecht, studierichting klinische psychologie. Tijdens haar bacheloropleiding studeerde ze een semester aan de Universiteit van Alberta in Edmonton (Canada) en voltooide ze met succes het Von Humboldt honoursprogramma. In 2013 begon ze aan haar master Klinische en Gezondheidspsychologie aan de Universiteit Utrecht. Haar klinische masterstage liep ze bij de afdeling Medische Psychologie en Maatschappelijk Werk van het Wilhelmina Kinderziekenhuis, Universitair Medisch Centrum (UMC) Utrecht. Nadat ze in 2014 cum laude afstudeerde, werkte ze aan meerdere klinische en onderzoeksprojecten in Nederland en Stellenbosch (Zuid-Afrika). In 2016 begon ze aan haar promotieproject op de afdeling Kinder- en Jeugdpsychiatrie/ Psychologie van het Erasmus MC - Sophia Kinderziekenhuis in Rotterdam, wat heeft geresulteerd in het werk dat in dit proefschrift is beschreven. Het project werd begeleid door prof. dr. E.M.W.J. Utens, dr. I.M. van Beynum en, vanaf 2017, door prof. dr. M.H.J. Hillegers. Tijdens de afronding van haar proefschrift begon ze in september 2018 aan verschillende onderzoeksprojecten bij De Bascule, Academisch Centrum voor Kinder- en Jeugdpsychiatrie en het Amsterdam UMC. Sinds november 2019 werkt ze als postdoctoraal onderzoeker op de afdeling Kinder- en Jeugdpsychiatrie van het Amsterdam UMC. Malindi woont in Culemborg met Abe.

PHD PORTFOLIO

Name PhD student:	Malindi van der Mheen
Erasmus MC department:	Child and Adolescent Psychiatry/Psychology
Research school:	NIHES
PhD period:	May 2016 – Sept. 2018 (0.8 fte) and Oct. 2018 – April 2019 (0.4 fte)
Promotors:	Prof. dr. E.M.W.J. Utens Prof. dr. M.H.J. Hillegers
Supervisor:	Dr. I.M. van Beynum

1. PhD training	Year	Workload (ECTS)
General academic skills		
· Systematic Literature Retrieval in PubMed, Medical library Erasmus MC	2016	0.3
· EndNote, Medical library Erasmus MC	2016	0.3
· CPO Patient Oriented Research: design, conduct and analysis, Erasmus MC	2017	0.3
· Research Integrity, Erasmus MC	2017	0.2
· Basiscursus Regelgeving Klinisch Onderzoek, Nederlandse Federatie van UMC's	2017	1.0
· Biomedical English Writing and Communication, Erasmus MC	2017-2018	4.0
· Presenting skills for junior researchers, MolMed	2018	1.0
Specific research skills		
· LimeSurvey and GemsTracker, Erasmus MC	2016	0.3
· Regression Analysis, NIHES	2017	1.9
· Introduction to R	2018	0.1
· Repeated Measurements in Clinical Studies, NIHES	2018	1.9
Clinical training		
· CHIP-intervention protocol, Prof. Dr. McCusker & Dr. Doherty, Rotterdam, the Netherlands	2016	1.0
Workshops		
· Publications to find and how to be found, PhD Day, Erasmus MC	2017	0.1
· Presentation skills, TULIPS day, Culemborg, the Netherlands	2017	0.1
· Informed consent for children, TULIPS day, Culemborg, the Netherlands	2017	0.1
· Defend your PhD, Erasmus MC	2018	0.1
· Defend your thesis, PhD Day, Erasmus MC	2018	0.1

International and national conferences and presentations		
· Association for European Paediatric and Congenital Cardiology (AEPC) psychosocial conference, Rotterdam, the Netherlands (attendee)	2016	1.0
· Research work meeting Child and Adolescent Psychiatry/Psychology, Erasmus MC (oral presentation)	2016	0.2
· Meeting Pediatric Cardiology, Erasmus MC (oral presentation)	2016	0.2
· Symposium Pediatric Psychology Network the Netherlands (PPN-NL), Utrecht, the Netherlands (attendee)	2016	0.3
· Club van 100, Fonds NutsOhra, Amsterdam, the Netherlands (poster presentation)	2016	0.3
· PPN-NL, Utrecht, the Netherlands (oral presentation)	2017	0.3
· Club van 100, Fonds NutsOhra, Rotterdam, the Netherlands (attendee)	2017	0.3
· Dutch association for cognitive and behavioral therapy, Veldhoven, the Netherlands (oral presentation)	2017	1.5
· Research meeting Pediatric Psychology, Erasmus MC (oral presentation)	2017	0.2
· Science café Child and Adolescent Psychiatry/Psychology, Erasmus MC (oral presentation)	2018	1.0
· Research work meeting Child and Adolescent Psychiatry/Psychology, Erasmus MC (oral presentation)	2018	0.2
· AEPC psychosocial conference, Leicester, United Kingdom (oral presentation)	2018	2.0
· Colloquium Child- and Adolescent Psychiatry, Erasmus MC (oral presentation)	2018	0.3
· Sophia Research Day, Erasmus MC (oral presentation; first prize)	2018	1.0
· Capita Selecta Pediatric Cardiology, Erasmus MC (oral presentation)	2018	0.3
· AEPC medical conference, Athens, Greece (oral presentation)	2018	2.0
· Cadiac Neurodevelopmental Outcome Collaborative, Kansas, United States (poster presentation)	2018	2.5
· European Pediatric Psychology Conference, Ghent, Belgium (oral presentation)	2018	2.0
· Australian Psychological Association, Sydney, Australia (oral presentation)	2018	2.0
· Science café Child and Adolescent Psychiatry/Psychology, Erasmus MC (oral presentation)	2019	1.0
Other		
· Research work meetings Child and Adolescent Psychiatry/Psychology, Erasmus MC (attendee; biweekly)	2016-2019	3.0
· Research meetings Pediatric Psychology, Erasmus MC (attendee; 4 times a year)	2016-2019	1.0
· Science café Child and Adolescent Psychiatry/Psychology, Erasmus MC (attendee; monthly)	2017-2019	2.0
· Symposium Ron van Domburg, Rotterdam, the Netherlands (attendee)	2016	0.3

· Symposium Frank Verhulst, Rotterdam, the Netherlands (attendee)	2017	0.3
· PhD Day Erasmus MC (attendee)	2017	0.3
· PhD Day Erasmus MC (attendee)	2018	0.3
· Patient day, Erasmus MC (interview)	2018	0.3
2. Teaching		
Medical students		
· Practical: Observation techniques	2017	1.0
· Practical: Social interaction	2018-2019	1.5
· Practical: Oppositional behavior	2018	1.0
· Writing a systematic review	2017-2018	1.0
Supervising Master's theses and research interns		
· Deanne Obbink (Clinical Child and Adolescent Psychology, Erasmus University): The level of stress and worry of parents of children with congenital heart disease	2017	3.0
· Heleen Berenschot	2016-2017	1.0
· Anastasiya Burdina	2017	1.0
Supervising Bachelor's theses		
· Esther Stoop (Psychology, Erasmus University): Psychosocial well-being of children with congenital heart disease: A literature review	2018	1.0
· Marloes Rijnsaardt (Psychology, Erasmus University): Hersenontwikkeling in pasgeborenen met een aangeboren hartafwijking	2018	1.0
· Shivani Mahadew (Psychology, Erasmus University): De integratie van het psychosociaal welzijn in de behandeling van kinderen met een aangeboren hartafwijking	2018	1.0

ECTS – European Credit Transfer and Accumulation System

1 ECTS represents 28 hours