An Exercise Program in Youngsters with Complex Congenital Heart Disease: does it improve Health Related Quality of Life and Psychosocial Functioning? A randomized controlled trial.

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An Exercise Program in Youngsters with Complex Congenital Heart Disease: does it improve Health Related Quality of Life and Psychosocial Functioning?
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Een sport programma voor jongeren met een complexe aangeboren hartafwijking: verbetert het de kwaliteit van leven en het psychosociaal functioneren?
Een gerandomiseerd gecontroleerd onderzoek

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CONTENTS

Chapter 1

General Introduction

CONGENITAL HEART DISEASE

Congenital heart disease (ConHD) is the most common congenital malformation present at birth. ConHD is a developmental abnormality involving structures of the heart or the intra-thoracic great vessels. Nowadays, at least 95% of children born with ConHD survive into adulthood[1]. Some patients have mild defects, for which cardiac surgery is not needed. However, a majority of patients need cardiac surgery. After surgery, most repaired lesions have the potential for residua and sequelae. In these patients, aerobic fitness may be reduced, resulting in an inactive lifestyle[2]. An inactive lifestyle is associated with the occurrence of cardiovascular disease, with an increased risk of death, and with a poorer health related quality of life (HRQoL)[3]. Therefore, during the last decades, research has focused not "only" on morbidity and mortality, but also on the impact of residua of ConHD on quality of life and psychosocial functioning of children and adolescents[4].

In this thesis, a randomized controlled trial (RCT) is described in which the effects of an exercise program on HRQoL and psychosocial functioning in youngsters with ConHD are investigated. The children, adolescents, and young adults that participated in this RCT underwent cardiac surgery for tetralogy of Fallot or they underwent surgery for one of the diagnoses referred to as univentricular hearts, the Fontan procedure.

TETRALOGY OF FALLOT

Tetralogy of Fallot (ToF) is a combination of four heart defects[5]. The key abnormality in this defect is an anterior deviation of the outlet septum, resulting in 1) a ventricular septal defect (VSD); a developmental abnormality in any proportion of the ventricular septum resulting in abnormal communications between the two lower chambers of the heart; 2) pulmonary stenosis, this is the pathologic narrowing of the communication of the right ventricle and the pulmonary artery, at the level of the right ventricular infundibulum or the opening of the pulmonary valve. This restricts the blood flow from the right ventricle to the pulmonary artery; 3) right ventricular hypertrophy, a thickening of the wall of the right ventricle; 4) override of the aorta over the ventricular septum.

Most children born with ToF are cyanotic because oxygen poor blood may flow from the right ventricle directly into the aorta, which reduces the oxygen saturation in the aorta. A feature of cyanosis is a bluish discoloration of the skin and mucous membranes due to an increase in the amount of deoxygenated hemoglobin in the blood.

FONTAN PROCEDURE

Nearly 10% of the children born with ConHD belong to the heterogeneous group of patients with functionally univentricular hearts[6]. Biventricular repair is precluded in these children. Therefore they are treated with the Fontan operation: a palliative procedure. An example of a cardiac defect for which the Fontan procedure is required is hypoplastic left heart syndrome. This is a condition caused by underdevelopment of the whole left half of the heart.

Nowadays, the Fontan operation is performed as a staged procedure. In most cases at least 2 major operations are necessary, resulting in redirection of the systemic venous return to the pulmonary circulation without interposition of a subpulmonary ventricle. Currently, total cavopulmonary connection, with either an intra-atrial lateral tunnel or an extra-cardiac conduit, is the preferred procedure[7]. Since the use of this procedure, mortality and morbidity have improved dramatically in the last decades.

PHYSICAL LIMITATIONS IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH COMPLEX CONHD

Children, adolescents, and young adults with ToF, with right ventricular loading abnormalities, or those with a Fontan circulation, with single ventricle lesions, may experience long-term physical morbidity. They are at great risk for heart failure[8], their exercise capacity may be reduced, and they do not participate in the same amount of (dynamic) physical activity as their healthy peers[9-11]. In addition, their physical inactivity is associated with a poorer HRQoL[3].

These children, adolescents, and young adults with ToF or with a Fontan circulation may benefit from an exercise program. Until now, only a few small, non-randomized studies indicated that participation in an exercise program improved exercise capacity and physical activity in these children and adolescents[12].

AN EXERCISE PROGRAM IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH CONHD; PHYSICAL OUTCOMES

The effects of an exercise program in children, adolescents, and young adults with ConHD on physical outcomes, such as peakVO_2, activity levels, and muscle strength have recently been systematically reviewed[12]. A total of 31 studies were included. These studies provided actual evidence for effects of an exercise program in patients with congenital heart disease, age range 4 – 45 years. Most studies used 12-week programs with 3 training sessions per week.

The overall conclusion was that most studies reported significant improvements on peakVO_2, activity levels, or muscle strength. Besides, none of the studies reported negative physical effects of the exercise programs. However, most of these studies were performed in small heterogeneous patient groups.

Although an exercise program improved HRQoL in adults with ConHD[13], effects of an exercise program on HRQoL in children and adolescents with ConHD were generally not reported. Furthermore, associations between, on the one hand, physical fitness and exercise programs, and, on the other hand, HRQoL and psychosocial functioning in children and adolescents, also remained unclear.

ASSOCIATIONS BETWEEN PHYSICAL ACTIVITY, EXERCISE CAPACITY, AND PSYCHOSOCIAL FUNCTIONING

In 2013 a systematic review by Dulfer et al.[14] was published regarding the associations between exercise capacity, physical activity, respectively an exercise program, and psychosocial functioning of children and adolescents with ConHD. This review is presented in this thesis as Chapter 2[14].

Summarizing, in most studies, exercise capacity was strongly associated with physical domains of quality of life (QoL). In contrast, exercise capacity was hardly associated with psychosocial domains of QoL.

Interestingly, although an exercise program improved exercise capacity in children with ConHD, its influence on QoL and psychosocial functioning was only reported on in a few studies. Although exercise capacity was barely associated with psychosocial parameters, these studies, which shared methodological limitations, found promising results. Therefore we tried to replicate these findings in a randomized controlled trial with a relatively large sample, using a standardized exercise program and standardized instruments to assess HRQoL and psychosocial functioning.

PSYCHOSOCIAL OUTCOMES

Health related quality of life

Since most of the children born with ConHD nowadays survive into adulthood[15], HRQoL has become an important outcome in paediatric cardiology health care, and also in research. HRQoL, however, is still an ambiguous concept and consensus about is definition is lacking[16]. The World Health Organization defines health as: "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (World Health Organization, 1948). The terms health status and HRQoL are often used interchangeably. However,

health status refers to assessment of a persons' actual, more objective problems and limitations, whereas HRQoL assessment includes a persons' subjective, emotional evaluation of such problems and limitations.

In this thesis, HRQoL in children and adolescent with ConHD was approached as a multidimensional assessment construct, including physical health, psychological state, and social relationships. HRQoL is assessed as children's health status problems, supplemented with their emotional response to these problems[4]. Since perspectives of children and parents may differ, a multi-informant approach (parent-report and child-report) was used in this study to assess HRQoL. A comprehensive evaluation was obtained from these different perspectives[17].

Emotional and behavioural problems

Children with ConHD are at risk for elevated levels of emotional and behavioural problems[18], especially internalizing problems (e.g. anxiety and depression). As to the treatment of internalizing problems, cognitive behavioural methods as well as psychotropic medications are used. Cognitive behavioural therapy is an evidence-based treatment of anxiety and depression in medically ill children and adolescents[19]. On the other hand, in children and adolescents from the general population, improvements in cardiorespiratory fitness also had positive effects on depression, anxiety, mood status, and self-esteem[20].

Until now, only one non-randomized study has tested the effects of an exercise program on emotional and behavioural problems in children with various diagnoses of ConHD[21]. This study used two exercise programs: a 2 weeks program in a rehabilitation centre or a 5 months home-based program (called "interventions"). Outcomes were compared with those of voluntary controls with ConHD.

Both intervention parents and control parents reported fewer externalizing problems and social problems in their child. Only intervention parents reported fewer internalizing problems at post-treatment assessment. On patients' self-reports no significant effects were found at post-assessment. Shortcoming of this study was that it was not a randomized controlled trial; children who did not want to exercise were assigned to the control group. Besides, the exercise program encompassed two elements: training in a centre or self-training at home. Training periods of these 2 elements differed. However, outcomes of these two intervention elements were analysed as one intervention group.

Considering the lack of systematic studies in this field, a randomized controlled trial assessing effects of standardized an exercise program on emotional and behavioural problems has surplus value.

Sports enjoyment and leisure time spending

Adults with ConHD have a higher risk for complications, e.g. cardiovascular disease, than adults in the general population[22]. To prevent or postpone these complications, it is important to pursue a healthy life style; e.g. participate in sports and physical activity during leisure time. Healthy life styles are commonly formed in adolescence and persist into adulthood[23]. Therefore, 'evidence-based' interventions to stimulate healthy life styles should become available for adolescents with ConHD.

In the general population, sports enjoyment is one of the main reasons for adolescents to participate in sports and physical activities[24]. Unfortunately, qualitative research has revealed that adolescents with ConHD see sports rather as an instrumental purpose, as being important because of its health benefit, than as being enjoyable[25].

Since it is unknown whether participation in an exercise program may improve sports enjoyment and active leisure time spending in adolescents with ConHD, these outcomes were investigated in the present study.

Parental moderators

Parents of children with ConHD have been described as overprotective and anxious, which may hamper participation of their children in physical activities and sports[26, 27]. Since parental mental health and parental worries were related to emotional adjustment in children with ConHD[28, 29], these parental variables may moderate effects of an exercise program in their children. Social support (e.g. family support) is also known to be associated with HRQoL in adolescents and adults with a Fontan circulation[30]. Therefore, parental support, specifically regarding sports, was included as a moderator in this study.

THE PRESENT STUDY: A MULTICENTRE RANDOMIZED CONTROLLED TRIAL

The aim of the study, described in this thesis, is to investigate the effects of a standardized exercise program on HRQoL and psychosocial functioning in children, adolescents, and young adults, aged 10 – 25 years, with tetralogy of Fallot (ToF) or with a Fontan circulation.

Inclusion/exclusion

Included were patients, aged 12 to 20, who underwent cardiac surgery before the age of 2 years for ToF, and patients, aged 10 to 25, who underwent surgery for single-ventricle physiology (intra-cardiac or extra-cardiac tunnel type of Fontan-completion, with at least 2 stages) before the age of 6 years.

Patients were treated at one of the 5 participating centres of paediatric cardiology in the Netherlands: Academic Medical Centre Amsterdam, Erasmus Medical Centre Rotterdam, Leiden University Medical Centre, University Medical Centre Radboud Nijmegen, and University Medical Centre Utrecht.

Excluded were patients with: contra-indications for exercise, mental retardation, standard contra-indications for MRI, or a ventricular outflow obstruction (peak Doppler gradient > 60 mm Hg).

Randomization

After informed consent had been obtained, patients received an anonymous study code and were invited for medical and psychological *baseline* assessments. After that, a 'blind' independent researcher allocated the patients to the exercise program or the control group (ratio 2:1) according to restricted block randomization. Every participant that was enrolled in the study was stratified by age, gender, and cardiac diagnosis into a specific group. The first enrolled patient and the second enrolled patient in that specific stratification group (e.g. age-group 10-12, boys, Fontan) were randomized through envelopes into the exercise group or in the control group. The randomization of the third enrolled patient in that specific stratification group was dependent of the previous two randomizations in that specific stratification group.

Intervention

The standardized exercise program consisted of 3 training sessions of 1 hour per week, during a 12-week period. Patients who already participated in sports activities were instructed to continue these activities and participate in the exercise program 2 times a week. The exercise program consisted of 10 minutes warming-up, 40 minutes aerobic dynamic cardiovascular training, and 10 minutes cooling down. Participants were given a heart rate monitor to perform their exercises within the given heart range (resting heart rate plus 60-70 % of the heart rate reserve). This range was determined by an ergometer-test performed at the baseline assessment.

The program was performed group-wise, under supervision of a trained and licensed physiotherapist in local centres throughout the Netherlands. The same researcher (ND) visited all participating physiotherapists prior to the start of the program and visited them thereafter when needed, to ensure standardized implementation of the exercise program. The control group continued their normal daily live and were invited for a baseline and a follow-up medical and psychological assessment. In this thesis the outcomes of the psychological assessments were described.

Assessment procedure

The ethics-committee review boards of all 5 medical centres approved the research protocol. All eligible patients and their parents were approached uniformly through a patient-information letter and completed the same psychological instruments at 2 points in time.

The baseline psychological assessment, a *web-based* questionnaire and a semi-structured interview by phone, took place no longer than 2 months before the start of the exercise program, and 1-3 days before the baseline cardiac assessment in the hospital.

The second psychological assessment was performed no later than one month after completion of the exercise program, and no later than 2 weeks after the second cardiac assessment in the medical centre. Assessments for control groups were performed at comparable timepoints.

Web-based questionnaire

The web-based questionnaire, a child-version and a parent-version, encompassed where possible standardized assessment instruments with good psychometric properties, such as reliability and validity.

Child variables

Health related quality of life

To assess generic aspects of HRQoL in children aged 10 – 15, we used *The TNO/AZL Child Quality of Life Questionnaire (TACQOL),* Child Form (CF) and Parent Form (PF)[31].

In adolescents and young adults, aged 16 – 25, we assessed subjective health status with the self-reported generic *SF-36 Health Survey (SF-36)*[32]. In these adolescents/young adults, we also assessed cardiac-specific aspects of HRQoL with the self-reported *Congenital Heart Disease-TNO/AZL Adult Quality of Life (CONHD-TAAQOL)*[15].

In all children, adolescents, and young adults, self-perceived QoL was measured with the *Linear Analogue Scale (LAS)*[33].

Emotional and behavioural problems

To assess emotional and behavioural problems in children and adolescents aged 12 – 17, we used the parent-reported *Child Behavior Checklist* (CBCL) and the self-reported *Youth Self-Report* (YSR)[34].

To assess anxiety for sports, we used the self-reported *anxiety thermometer* (AT), which is derived from the Anxiety Disorders Interview Schedule[35].

Sports enjoyment

Self-reported sports enjoyment was assessed in children, adolescents, and young adults, with the *Groningen Enjoyment Questionnaire*[36].

Health behaviour

The Rotterdam Health Behaviour Questionnaire (RHBQ) was specifically designed for this study to assess health behaviour in children, adolescents, and young adults. This self-reported questionnaire was based on the Annual Report 2012 National Youth Monitor[37] and Youth Risk Behaviour Surveillance System[38].

Parent variables

Parental mental health was assessed with the *General Health Questionnaire-28* (GHQ-28)[39, 40].

Parental social support for exercise was assessed with the Dutch version of the *Social Support for Diet and Exercise*[41, 42]. For this study we used one scale: Family support for Exercise Habits Scale: Participation and Involvement (SSE).

Semi-structured interview

A semi-structured interview was completed by phone. Separate questions were included for children, aged 10 – 15, adolescents/young adults, aged 16 – 25, and for parents of children/adolescents, aged 10 – 17. In these interviews biographical data, such as household composition, educational level, and social participation were assessed. In addition, leisure time spending and disease knowledge were assessed.

Leisure time spending

Self-reported leisure time spending was assessed in all participants with *The Rotterdam Leisure-time Spending Questionnaire* (RLSQ)[43], which was based on data obtained from the Dutch Central Bureau for Statistics[37].

Disease knowledge

The Rotterdam Knowledge Questionnaire (TRKQ)[44] was based on Leuven Knowledge Questionnaire for Congenital Heart Disease[45]. Disease knowledge was assessed in all participants, and in their parents.

THE STRUCTURE OF THIS THESIS

The aim of this thesis is to investigate the effects of a standardized exercise program on HRQoL and psychosocial functioning in children, adolescents, and young adults, aged 10 – 25 years, with tetralogy of Fallot (ToF) or with a Fontan circulation. In *chapter 2*, studies into

the associations between exercise capacity, physical activity, and psychosocial functioning in children and adolescents with ConHD were systematically reviewed. In *chapter 3*, the effects of an exercise program on health related quality of life in children, adolescents, and young adults aged 10 – 25 were investigated. In *chapter 4*, the effects of an exercise program on emotional and behavioural problems in children and adolescents aged 10 – 17 were examined. In *chapter 5*, the effects of an exercise program on sports enjoyment and leisure time spending in children, adolescents, and young adults aged 10 – 25 were assessed. We also identified moderating influence of health behaviour and disease knowledge. In *chapter 6*, the moderating influence of parental mental health and parental social support for exercise on pre-post changes in HRQoL in children and adolescents, aged 10 – 15, with ConHD were investigated. Finally, in *chapter 7,* the main findings and conclusions of this thesis are discussed. Clinical implications for medical practice and implications for future research are given.

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Chapter 2

Associations between exercise capacity, physical activity, and psychosocial functioning in children with congenital heart disease: A systematic review

Karolijn Dulfer, Willem A. Helbing, Nienke Duppen, Elisabeth M.W.J. Utens

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ABSTRACT

Background

Children and adolescents operated upon for congenital heart disease (ConHD) may show reduced exercise capacity and physical activity, possibly associated with lowered self-esteem and quality of life (QoL). The studies into associations between these parameters have not been reviewed before.

Objective

Review of studies into associations between exercise capacity, physical activity, respectively an exercise program, and psychosocial functioning of ConHD youngsters.

Data sources

PubMed, Embase and reference lists of related articles.

Study selection

Articles published between January 2000 and December 2012 into exercise capacity and/or physical activity, and a measure of psychosocial functioning in children with ConHD.

Data extraction

Two investigators independently reviewed the identified articles for eligibility, and one author extracted the data.

Results

Although exercise capacity was strongly related to physical domains of parent-reported and self-reported QoL, it was almost never associated with psychosocial domains of QoL. Physical activity was rarely associated with physical or psychosocial domains of QoL. Remarkably, self-reported depressive symptoms were associated with both physical and psychosocial QoL. The few studies into exercise programs showed promising results as to QoL and emotional and behavioural problems, but they contained methodological flaws.

Conclusions

No clear relationships were found between exercise capacity, physical activity, and QoL in children and adolescents with ConHD. Therefore we recommend assessing QoL separately, preferably both self-reported and parent-reported. Since depressive symptoms were associated with reduced physical and psychosocial QoL, screening on these symptoms is also recommended.

INTRODUCTION

Children and adolescents operated upon for congenital heart disease (ConHD) may show long-term morbidity as reflected by reduced exercise capacity[1], lower physical activity level[2], lower self-esteem and health related quality of life (HRQoL)[3-6]. Physical limitations may lead to social isolation and fewer possibilities to develop social competencies.

Using community samples, two reviews into the association between physical activity and mental health outcomes in children and adolescents showed that physical activity improved mental health, reduced depressive symptoms, and enhanced self-esteem[7, 8]. As to children and adolescents with ConHD, Takken et al.[9] formulated recommendations for participation in leisure sports, physical activity, and exercise programs for optimal physical, emotional, and psychosocial development. Tikkanen et al.[10] performed a systematic review into the influence of paediatric cardiac rehabilitation on exercise capacity and physical activity, showing many physical benefits from cardiac rehabilitation. To our knowledge, however, no review regarding the *associations* between exercise capacity, physical activity, and *psychosocial* functioning of ConHD children and adolescents has been performed.

This review is the first to fill in this gap in knowledge by giving an overview of studies investigating the association between exercise capacity, physical activity, and psychosocial functioning of ConHD youth. This review also includes the few studies addressing the influence of an exercise program on psychosocial functioning in children with ConHD.

METHODS

Search strategy

Because of the improved medical treatment of ConHD during the last decades, the search strategy was limited to the time period January 2000 to December 2012.

We searched the following electronic databases for articles published in English: 1) EMBASE and 2) PUBMED, using the search terms: a) "congenital heart disease" as Emtree/MESH term and all types of "congenital heart disease" as abstract-title terms, b) "children" and/or "adolescents" (age range 6-18) as Emtree/MESH term, all sub-terms apart as abstract-title terms, c) "physical activity", "capacity" and "performance" as Emtree/MESH terms and all sub-terms apart as abstract-title terms. Additional studies were obtained from the references of the selected articles. Then we screened whether a construct of psychosocial functioning was measured in the titles and/or abstracts of all articles found through the search strategy.

Data collection

For all eligible studies the following variables were determined: sample size, age range, complexity of ConHD, use of control groups, type of tests to assess exercise capacity and physical activity, objectively or subjectively assessed, type of instruments to assess psychosocial functioning, self-reported or parent-reported. Complexity of ConHD was based on the classification as proposed by Warnes et al.[11].

As psychosocial functioning is such a broad construct, assessed with different types of questionnaires, for different age groups and informants, a statistical workup with a meta-analysis was not possible.

Exercise variables: exercise capacity and physical activity

In this review, two physical parameters, 'exercise capacity' and 'physical activity', were considered to be predictor variables of psychosocial functioning in ConHD children.

Exercise capacity is objectively assessed with a cardiopulmonary exercise test[12]. This test is often used in the standard care of children with congenital heart disease. Most studies described in this review used either a treadmill test or a bicycle test. Both tests provide peak oxygen uptake (VO_2max), peak oxygen consumption at anaerobic threshold (VAT), or heart rate (HR) as outcomes. One study used parent-reported exercise[13].

Physical activity (PA) can be measured objectively or subjectively. It is measured objectively with a uni-axial or a multi-axial accelerometer; the multi-axial method provides a more precise outcome. Subjectively measured PA is self-reported and is therefore not always consistent with objectively measured PA[2].

Psychosocial functioning

The studies selected for this review assessed the following psychosocial constructs: 1) quality of life, 2) emotional and behavioural problems, 3) self-efficacy, and 4) depressive symptoms.

Quality of life *(QoL)* is an ambiguous concept and consensus about its definition is lacking[14]. The studies described in this review used different questionnaires to assess quality of life. The questionnaires can be categorized as: generic versus disease-specific[2, 15], focusing on symptoms per se versus on the subjective evaluation of these symptoms, and self-reported versus parent-reported.

Emotional and behavioural problems. Almost all studies in this area used the Child Behavior Checklist[13, 16, 17]; this parent-report contains questions about withdrawn behaviour, somatic complaints, anxious/depressed behaviour, thought problems, aggressive behaviour, delinquent behaviour, social problems, and attention problems in their child.

Self-efficacy was examined in 2 studies. They both used self-reported questionnaires with 1 item[18] or 8 items[19].

Depressive symptoms conceptually belong to the domain of emotional/behavioural problems. One study reported on these symptoms separately[20].

RESULTS

Initially we found 3,554 articles by using our search strategy. Based on titles and abstracts, one researcher (KD) excluded studies that did not investigate exercise capacity or physical activity in combination with psychosocial functioning. After this, we adjusted for the same articles found in both Pubmed and Embase. This resulted in 379 eligible articles. Then, the same researcher screened the full-text of these 379 articles on the predefined keywords: exercise capacity and/or physical activity, together with a psychosocial functioning construct. Studies containing solely adult patients, no more than a study design, unspecified assessment instruments, or a qualitative design, were also excluded; see figure 1.

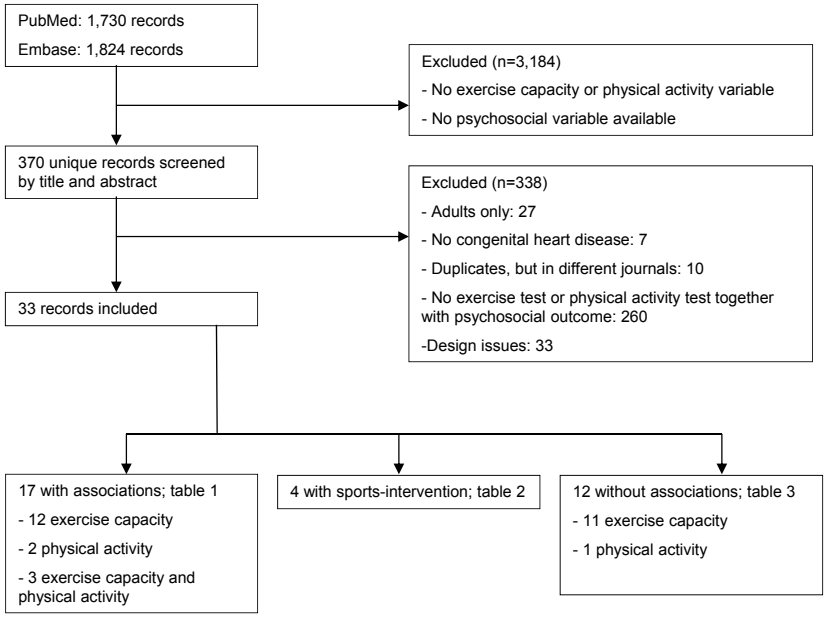

Figure 1: Flowchart study selection process

Two researchers reached consensus about the remaining articles and included a total of 33 articles in this review. The study characteristics of 17 studies into associations between exercise capacity, physical activity, and psychosocial functioning in children and adolescents

with ConHD are outlined in table 1. Four studies into influence of an exercise program on psychosocial functioning in children and adolescents with ConHD are outlined in table 2. In 12 studies exercise capacity, physical activity, and psychosocial functioning were measured, but specific associations were not investigated. These studies were considered to be important, but are only described in table 3.

Figure 2 visually shows association-arrows between physical variables, i.e. exercise capacity and physical activity, and psychosocial outcome variables. Each association-arrow contains correlations with, in brackets, the corresponding article numbers.

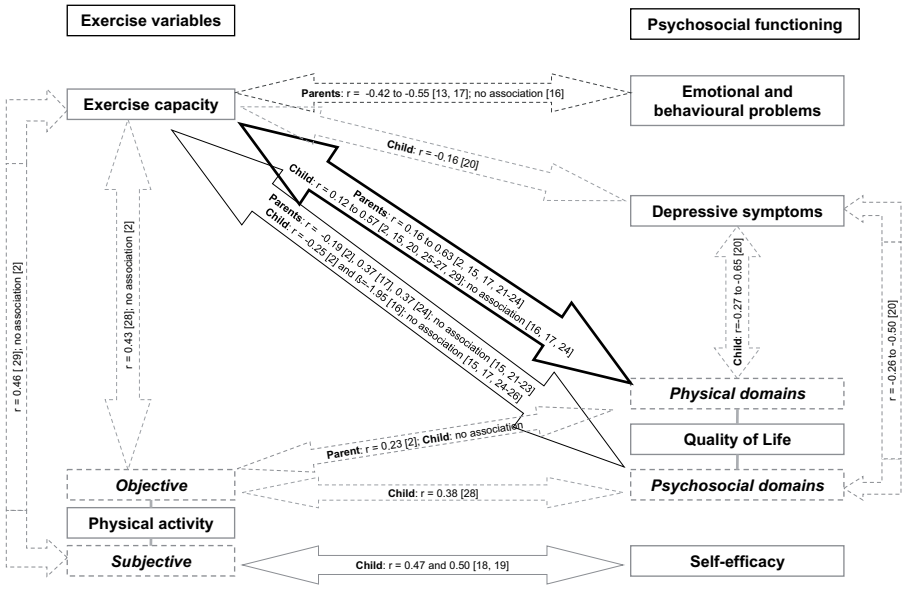

Figure 2: Associations between exercise variables and psychosocial outcomes

Exercise capacity and psychosocial functioning

Twelve of the 17 studies assessed exercise capacity as the only predictor variable together with a psychosocial outcome variable[13, 15-17, 20-27]; see table 1. Of these 12 studies, 8 assessed QoL, 2 assessed QoL and emotional and behavioural problems, 1 assessed emotional and behavioural problems, and 1 assessed QoL and depressive symptoms.

As to the 11 studies with QoL as outcome, 8 studies investigated the relationship between exercise capacity and self-reported QoL[15-17, 20, 24-27] and 6 assessed parent-reported QoL[15, 17, 21-24]. Regarding self-reported QoL, 5 out of 8 studies[15, 20, 25-27] reported that higher exercise

Table 1: 17 studies into associations between exercise capacity, physical activity, and psychosocial functioning in children and adolescents with congenital heart disease

				Exercise variables		Outcome variable	
Authors	**Sample (age-range in years)**	**Complexity of ConHD**	**Control group**	**Exercise capacity**	**Physical Activity**	**Psychosocial functioning**	**Results**
Exercise capacity							
Kwon, 2011[15]	22 TOF (8-18)	Moderate	-	VO2max (Treadmill)	-	Quality of life; PedsQL (c) + (p)	QoL scores for TOF children are similar to normative data, and higher than for other chronically ill children. Higher exercise capacity was associated with higher parent-reported physical QoL (r=0.63) and higher self-reported physical QoL (r=0.47). Parents reported lower QoL scores, relative to the child-reports.
Blaufox, 2008[21] *	404 Fontan (6-18)	Great	-	VO2max VAT Peak HR (Bicycle)	-	Quality of life; CHQ-PF50 (p)	Higher Peak HR (r=0.16) and lower peak HR (r=-0.18) were associated with higher parent-reported QoL physical scale score. Resting HR and peak HR were not associated with QoL psychosocial scale scores.
Williams, 2009[22] *	476 Fontan (6-18)	Great	-	VO2max (Bicycle)	-	Quality of life; CHQ-PF50 (p)	Higher exercise capacity was associated with higher parent-reported QoL physical score (r=0.24). VO2max, ventricular ejection fraction, BNP, and the QoL physical score were combined into a functional score. A higher functional score was associated with a higher socioeconomic status.
McCrindle, 2010[23] *	157 Fontan (6-18) with maximal effort on exercise test	Great		Workload VO2max Peak HR (Bicycle)	-	Quality of life; CHQ-PF50 (p)	Only higher maximum workload was associated with higher parent-reported QoL physical sum score (r=0.29). There was no association between any of the exercise capacity variables and parent-reported QoL psychosocial sum scores.

Table 1 *Continued*

				Exercise variables		Outcome variable	
Authors	**Sample (age-range in years)**	**Complexity of ConHD**	**Control group**	**Exercise capacity**	**Physical Activity**	**Psychosocial functioning**	**Results**
Jenkins, 2008[24]	42 HLHS (8-17)	Great	-	VO2max (Treadmill or Bicycle)	-	Quality of life; CHQ-PF50 (p) CHQ-CF87 (c)	Higher exercise capacity was associated with higher parent-reported physical functioning (r=0.51), role social/physical (r=0.37) and global health (r=0.49). No associations were found between exercise capacity and self-reported QoL.
Hager, 2005[25]	149 various ConHD; (14-60)	Moderate Great	-	VO2max (Bicycle)	-	Quality of life; SF-36 (c)	Higher exercise capacity was associated with a higher self-reported physical functioning (r=0.52) and a higher general health (r=0.31). It did not correlate with any other QoL scale.
Gratz, 2009[26]	564 various ConHD; (14-73)	Mild Moderate Great	53 healthy controls	VO2max (Bicycle)	-	Quality of life; SF-36 (c)	Higher exercise capacity was associated with higher self-reported physical functioning (r=0.44), general health (r=0.28), role-physical (r=0.14), and vitality (r=0.14). Disease severity did not influence these associations, apart from one exception. Cyanotic patients had a lower exercise capacity and physical functioning score, relative to other diagnoses.
Mueller, 2012[27]	168 TOF (8-16)	Moderate	-	Vo2max (Bicycle or Treadmill)	-	Quality of life; KINDL (c)	Higher exercise capacity was associated with higher self-reported physical well-being (r=0.26) and higher QoL total score (r= 0.17). There were no associations between exercise capacity and psychosocial QoL subscales.
Hovels-Gurich, 2002[16]	60 TGA ASO (7-14)	Great	-	Endurance capacity (Treadmill)	-	Emotional and behavioural problems; CBCL (p) Quality of life; IQLC (c)	In a prediction model, higher exercise capacity was associated with decreased self-reported stress from illness (ß=-1.95). No influence of exercise capacity on other IQLC scales, or on CBCL scales.

Table 1 *Continued*

				Exercise variables		Outcome variable	
Authors	**Sample (age-range in years)**	**Complexity of ConHD**	**Control group**	**Exercise capacity**	**Physical Activity**	**Psychosocial functioning**	**Results**
Hovels-Gurich, 2007[17]	20 TOF and 20 VSD (5-11)	Moderate	-	Endurance capacity (Treadmill)	-	Emotional and behavioural problems; CBCL (p) Quality of life; KINDL (c) + (p)	Higher exercise capacity was associated with less parent-reported Internalizing problems (r=-0.55), Externalizing problems (r=-0.55), and Total problems (r=-0.44). It was also associated with higher parent-reported physical status (r=0.42) and self-esteem (0.37). No associations were found between exercise capacity and self-reported QoL.
Fredriksen, 2004[13]	326 various ConHD (11-16)	Mild Moderate Great	-	Parent-reported exercise capacity	-	Emotional and behavioural problems; CBCL (p)	In a linear regression model, higher parent-reported exercise capacity was associated with lower parent-reported emotional and behavioural problem scales. Disease severity did not influence this association.
Muller, 2012[20]	767 various ConHD; (14-67)	Mild Moderate Great	-	Vo2max (Bicycle)	-	Quality of life; SF-36 (c) CES-D (c)	ConHD adolescents/adults had a lower prevalence of depressive symptoms (8,6%) than normative data. Higher exercise capacity was associated with higher physical functioning (r=0.39), higher general health (r=0.27), higher vitality (r=0.12), and with less depressive symptoms (r=-0.16). Less depressive symptoms were associated with higher physical and psychosocial QoL (r=-0.17 to -0.74).
Physical activity							
Bar-Mor, 2000[18]	100 trivial-to-moderate ConHD (12-18)	Mild Moderate	-	-	Self-reported physical activity; 1 item	Self-efficacy; 1 item (c)	Higher self-reported physical activity was associated with higher self-reported self-efficacy (r=0.50). The advice of the cardiologist regarding physical activity (PA) was associated with mother's attitude (r=0.84) respectively the child's self-efficacy (r=0.50) regarding physical activity.
Ray, 2011[19]	84 various ConHD (10-14)	Mild Moderate Great	-	-	Self-reported PA; 5 item YRBS (c)	Self-efficacy; 8-item (c)	Higher self-reported physical activity was associated with higher self-reported self-efficacy (r=0.47).

Table 1 *Continued*

				Exercise variables		Outcome variable	
Authors	**Sample (age-range in years)**	**Complexity of ConHD**	**Control group**	**Exercise capacity**	**Physical Activity**	**Psychosocial functioning**	**Results**
Exercise capacity and physical activity							
Muller, 2009[28]	57 univentricular heart physiology after TCPC (8-52)	Great	-	VO2max (Bicycle)	Minutes per day; Triaxial accelerometer	Quality of life ; CHQ-CF87(c) SF36 (c)	Higher exercise capacity was associated with higher physical activity (r=0.43). Daily activity of 72% of the patients was within recommendations. TCPC children < 9 years were less physical active than healthy peers. Only in ConHD children <14 years, higher objectively measured physical activity was associated with higher self-reported mental health scale (r=0.38).
McCrindle, 2007[2] *	147 Fontan (7-18)	Great	-	VO2max VAT (Bicycle)	Minutes per day; Uni-axial accelerometer Self-reported PA; questionnaire	Quality of life; CHQ-PF50(p) CHAT (c) #	Exercise capacity was not related to physical activity. A higher exercise capacity was associated with a higher parent-reported global health (r=0.39), less physical functioning limitations (r=0, 21), less impact of these limitations (r=0.21), less general behavioural problems (r=-0.19), higher general health (r=0.25), and a higher overall physical summary score (r=0.29). As to self-reported QoL, a higher exercise capacity was associated with a lower general health (r=-0.19), less activity limitations (r=-0.32), and less symptoms concern (r=-0.25). Objectively PA was not related to self-reported PA (r=-0.04). A higher physical activity was only associated with a higher parent-reported general health (r=0.23). As to self-reported QoL, a higher PA was, not significantly, associated with less self-reported activity limitations (r=-0.22) and less friendship concerns (r=-0.21).

Table 1 *Continued*

				Exercise variables		Outcome variable	
Authors	**Sample (age-range in years)**	**Complexity of ConHD**	**Control group**	**Exercise capacity**	**Physical Activity**	**Psychosocial functioning**	**Results**
Buys, 2012[29]	39 TGA AR (16-40)	Great	149 healthy controls	VO2max (Bicycle)	Self-reported PA; FPACQ	Quality of life; SF-36 (c)	Higher exercise capacity was associated with higher self-reported physical activity (r=0.46). Patients with TGA had lower scores on physical functioning and general health, and higher scores on bodily pain and several psychosocial domains than healthy controls. Higher exercise capacity was only associated with higher physical functioning QoL-score (r=0.57).

= disease specific questionnaire * For their analysis, all authors used the same cohort of Fontan children enrolled in the Paediatric Heart Network Fontan Cross-sectional Study**Congenital heart disease (ConHD)**

AR = arterial redirection, ASO = arterial switch operation, , ES = Eisenmenger syndrome , Fontan = Fontan circulation, HLHS = hypoplastic left heart syndrome, PS = pulmonary stenosis, TCPC= total cavopulmonary connection, TGA = Transposition of the great arteries, TOF = Tetralogy of Fallot, VSD = ventricular septal defect

Exercise capacity

HR= heart rate, VAT= peak oxygen consumption at anaerobic threshold, VO_2max= peak oxygen consumption

Physical activity (PA)

BQ = Baecke Questionnaire, FPACQ = Flemisch Physical Activity Computerizes Questionnaire

Psychosocial functioning

(p) = parent report, (c) = self-report

CBCL = Child Behavior Checklist, CES-D = Centre for Epidemiologic Studies Depression Scale, CHAT = Congenital Heart Adolescent or Teenage questionnaire, CHQ-CF87 = Child Health Questionnaire Child Form, CHQ-PF50 = Child Health Questionnaire Parent Form, IQLC = Inventory for the Assessment of the Quality of Life in Children and Adolescents, KINDL = Children Quality of Life Questionnaire, PedsQL-CF = Paediatric Quality of Life Inventory Child Form, PedsQL-PF = Paediatric Quality of Life Inventory Parent Form, SF-36 = 36 item short form, SH = sleeping habits, TACQOL-CF = TNO-AZL Child Quality of Life Questionnaire, YRBS = Youth Risk Behaviour Surveillance System, YSR = Youth Self Report

Other measurements

BNP = brain natriuretic peptide

capacity was associated with better physical QoL; i.e. better physical functioning, general health, or vitality. In addition, 1 study showed that higher exercise capacity was associated with better psychosocial QoL; i.e. less stress from illness[16]. As to parent-reported QoL, all 6 studies reported that higher exercise capacity was associated with higher physical QoL sum scales[15, 17, 21-24]. However, as note of caution, it must be mentioned that three[21-23] of these 6 studies reported on the same cohort of Fontan children, making it more difficult to make generalizations based on outcomes. Only 1 study[17] found that higher exercise capacity was associated with higher parent-reported self-esteem in their child.

Regarding the relationship between exercise capacity and parent-reported emotional and behavioural problems, 2 (of 3) studies[13, 17] reported that higher exercise capacity was associated with less parent-reported internalizing, externalizing, and total emotional and behavioural problems. The third study[16] did not find this association. Remarkably, Fredriksen et al.[13] used parent-reported exercise capacity instead of objectively assessed exercise capacity.

One study reported on the association between exercise capacity and both self-reported depressive symptoms and QoL[20]. It showed that higher exercise capacity was associated with less self-reported depressive symptoms and higher physical QoL. Moreover, better scores on self-reported physical and psychosocial QoL were associated with less self-reported depressive symptoms.

In sum: almost all studies reported that higher exercise capacity was associated with higher physical QoL. Exercise capacity was seldom associated with psychosocial domains of QoL. Higher physical and psychosocial QoL were associated with less depressive symptoms.

Physical activity and psychosocial functioning

In two studies, self-reported physical activity was assessed as the only predictor variable[18, 19]. Both studies showed that higher self-reported physical activity was related to better self-reported self-efficacy.

Relationship between both exercise capacity and physical activity and psychosocial functioning

Three studies assessed both exercise capacity and physical activity as predictor variables(2, 28, 29). Muller et al.[28] reported that only in children younger than 14, higher exercise capacity was associated with higher objective physical activity and higher scores for self-reported mental health. In contrast, the study of McCrindle et al.[2] showed no significant association between exercise capacity and objective physical activity. In addition, higher exercise capacity was associated with higher scores for parent-reported physical QoL and self-reported physical QoL. Higher physical activity was associated with higher parent-reported general

health only. Noteworthy: no association was found between objectively assessed physical activity with an accelerometer and self-reported physical activity with a questionnaire. In the third study[29] higher exercise capacity was associated with higher self-reported physical activity. Furthermore, higher exercise capacity was associated only with higher self-reported physical functioning.

In summary, the associations between exercise capacity, objective physical activity, and subjective physical activity were not consistent. Again, higher exercise capacity was associated with higher physical QoL. Only one study[2] reported an association between higher objective physical activity and better parent-reported general health.

Studies into an exercise program

Four studies investigated the effects of an exercise program on psychosocial functioning in adolescents with ConHD, see table 2. Fredriksen et al.[30] assigned 55 children with various ConHD to either a 2-week exercise intervention at a rehabilitation facility, or to a 5-month twice a week exercise intervention at a facility near their home. They compared them with 38 voluntary control children with ConHD. Exercise capacity improved in the entire exercise intervention group, but not in the control group. Physical activity improved in both the intervention and the control group. Reported by 27 parents of intervention children and 25 parents of control children, externalizing and total emotional/behavioural problems decreased post-treatment. Only in the exercise intervention group, parents also reported less internalizing problems, indicating that after treatment, their children showed e.g. less parent-reported anxiety/depression or withdrawn behaviour. There were no effects on self-reported emotional/behavioural problems in intervention and control children.

Rhodes et al.[31] studied 16 children with various ConHD who participated in a 12-week twice a week exercise program. At 1-year follow-up, these children had a sustained improved exercise capacity. The 18 voluntary control children did not. In contrast, the self-reported QoL scores did neither improve in the children who exercised nor in the control children. Moons et al.[32] showed that in 16 children with various ConHD, after attending a 3-day multi-sports camp, scores improved on self-reported physical functioning, role functioning due to emotional problems, role functioning due to behavioural problems, general behaviour, and mental health. In a replication study, Moons et al.[33] again found improvements in 25 children with various ConHD in several domains: physical functioning, role functioning due to physical or emotional problems, general health, self-esteem, mental health, and general behaviour directly after a 3-day multi-sports camp. However, at the 3-months follow-up, only the improvements on physical functioning and role functioning due to emotional problems sustained. Remarkably, parent-reported physical activity did not improve directly after

Table 2: 4 studies into the influence of an exercise program on psychosocial functioning in children and adolescents with ConHD

Author	Sample (age range)	Control group	Instruments	Procedure and intervention	Results
Fredriksen, 2000[30]	55 various ConHD (10-16)	38 ConHD controls	*Exercise capacity*; VO2max (treadmill) *Physical activity*; Accelerometer *Parent-reported emotional and behavioural problems*; YSR (c) CBCL (p)	T1 = baseline Two intervention-groups: - 2-weeks rehabilitation facility - 5 months, twice a week facility near home T2 = after intervention	Exercise capacity: VO2max only improved in intervention group. Physical activity: both intervention and control groups improved. Emotional and behavioural problems: both intervention and control parents reported less externalizing and social problems (CBCL). Only intervention parents reported less *internalizing* problems in their child from T1 to T2. No effects on self-reports (YSR) in the intervention and the control groups.
Rhodes, 2006[31]	15 severe ConHD (8-17)	18 ConHD controls	*Exercise capacity;* VO2max, Peak HR (bicycle) *Quality of life;* CHQ-CF87 (c) CHQ-PF50 (p)	T1 = baseline T2 = after a 12 week exercise program, twice a week. T3 = 1 year after T1	From T2 to T3, exercise capacity in the sports group remained improved, relative to T1. At T3, self-reported emotional, behavioural, and physical domains improved not significantly, but clinically meaningful. No findings for parent-reported QoL were mentioned. For all outcomes, there were no improvements in controls.
Moons, 2006a[32]	16 various ConHD (10-14)	-	*Quality of life;* CHQ-CF87 (c)	T1 = baseline; start sports camp T2 = after 3-day multi-sports camp	At baseline, physical functioning in ConHD children was lower relative to healthy peers. From T1 to T2: physical functioning, emotional role functioning, behavioural role functioning, general behaviour, and mental health scores improved. At T2: self-esteem and general behaviour in ConHD children was higher relative to healthy peers.

Table 2 *Continued*

Author	Sample (age range)	Control group	Instruments	Procedure and intervention	Results
Moons, 2006b[33]	25 various ConHD (10-15)	-	*Physical activity;* Baecke questionnaire (p) *Quality of life;* CHQ-CF87 (c)	T1 = baseline; start sports camp T2 = after 3-day multi-sports camp T3 = 3 months after T1	From T1 to T3, parent-reported physical activity did not improve. From T1 to T2, ConHD children scored higher on physical functioning, role functioning due to physical problems and due to emotional problems, general health, self-esteem, mental health, general behaviour. At T3, improvements on physical functioning and role functioning due to emotional problems sustained.

Table 3: 12 studies without associations into exercise capacity, physical activity, and psychosocial functioning in children and adolescents with congenital heart disease

				Exercise variables		Outcome variable	
Authors	**Sample (age-range in years)**	**Complexity of ConHD**	**Control group**	**Exercise capacity**	**Physical Activity**	**Psychosocial functioning**	**Results**
Exercise capacity							
Goldstein, 2011[36]	51 Fontan (10-18)	Great	22 healthy controls	VO2max (Treadmill)	-	Quality of life; PedsQL(c) + (p)	Exercise Capacity, self-reported QoL, and parent-reported QoL in Fontan children were lower, relative to healthy controls. There were no associations reported.
De Koning, 2008[37]	49 TGA ASO (5-14)	Great	33 healthy controls	Workload VO2max Peak HR (Bicycle)	-	Quality of life; TACQOL (c)	Exercise capacity, peak HR, QoL motor functioning and positive emotional functioning in TGA children were lower relative to healthy controls. No differences on other TACQOL scales. There were no associations reported.

Table 3 *Continued*

				Exercise variables		Outcome variable	
Authors	**Sample (age-range in years)**	**Complexity of ConHD**	**Control group**	**Exercise capacity**	**Physical Activity**	**Psychosocial functioning**	**Results**
Anderson, 2008[38] *	403 Fontan (6-18)	Great	-	VO2max VAT (Bicycle)	-	Quality of life; CHQ-PF50 (p)	Maximal exercise capacity of Fontan children was lower relative to healthy peers, and it varied with ventricular morphology. As to parent-reported QoL, physical and psychosocial scores were lower, relative to normative data. There were no associations reported
Atz, 2007[39] *	42 Fontan, heterotaxy syndrome (6-18)	Great	280 Fontan without heterotaxy	VO2max (Bicycle)	-	Quality of life; CHQ-PF50 (p) CHQ-CF87 (c) CHAT (c) #	Exercise capacity, parent-reported QoL, and self-reported QoL were the same in Fontan children with heterotaxy , relative to Fontan children without heterotaxy. With the disease specific QoL questionnaire,all Fontan children, with or without heterotaxy reported their general health to be excellent or very good, and their social life to be unaffected by their disease.
Atz, 2011[40] *	361 Fontan with fenestration (6-18)	Great	175 Fontan without fenestration	VO2max (Bicycle)	-	Quality of life; CHQ-PF50 (p)	Exercise capacity and parent-reported QoL were the same in Fontan children with fenestration, relative to Fontan children without fenestration.
Lambert, 2009[41] *	328 Fontan (10-18)	Great	-	VO2max (Bicycle)	-	Quality of life; CHQ-PF50 (p) CHQ-CF87 (c)	All domains of parent-reported QoL were lower relative to self-reported QoL, except for bodily pain. Lower parent scores for physical limitations domains, relative to their child, were not associated with exercise capacity.

Table 3 *Continued*

				Exercise variables		Outcome variable	
Authors	**Sample (age-range in years)**	**Complexity of ConHD**	**Control group**	**Exercise capacity**	**Physical Activity**	**Psychosocial functioning**	**Results**
Cohen, 2010[42]*	544 Fontan (6-18)	Great	-	Workload VO2max VAT (Bicycle)	-	Quality of life; CHQ-PF50 (p)	Relative to Fontan children with a midrange or low BMI, Fontan children with a high BMI scored lower on all exercise capacity measures. But their MRI and Echo findings and their parent-reported QoL scores were the same. Fontan children with a lower height had the same exercise capacity, but lower parent-reported QoL scores relative to Fontan children with a higher height.
Muller, 2011[43]	58 cyanotic patients + cardiac shunts (PS and ES) (14-55)	Great	-	Vo2max (Bicycle)	-	Quality of life; SF-36 (c)	Exercise capacity and QoL are lower in cyanotic patients relative to other diagnosis. Within cyanotic patients, patients with Eisenmenger syndrome have an even more impaired exercise capacity and QoL.
Muller, 2011[44]	28 TGA ASO + 28 TGA AR (>16 years)	Great	-	Vo2max Workload (Bicycle)	-	Quality of life; SF-36 (c)	Exercise capacity, self-reported physical functioning and general health of TGA ASO patients is higher than of TGA AR patients. For both groups, QoL scale-scores were comparable to normative data.
Lemmer, 2011[45]	81 right heart disease (mostly TOF) (6-43)	Moderate	31 healthy controls	Vo2max Peak HR (Treadmill)	-	Quality of life; SF-36 (c)	Relative to healthy controls, patients with right heart disease had a lower exercise capacity and had lower QoL scores, except for the bodily pain and general health scales. There were no associations reported.
Muller, 2011[46]	21 Ebstein anomaly pre-post surgery (6-59)	Moderate	-	Vo2max (Bicycle)		Quality of life; SF-36 (c)	After surgery for Ebstein anomaly, exercise capacity improved. QoL scores were good before and after surgery. Therefore, a higher exercise capacity did not result in higher QoL scores after surgery.

Table 3 *Continued*

				Exercise variables		Outcome variable	
Authors	**Sample (age-range in years)**	**Complexity of ConHD**	**Control group**	**Exercise capacity**	**Physical Activity**	**Psychosocial functioning**	**Results**
Physical activity							
Lunt, 2003[47]	153 various ConHD (12-18)	Mild Moderate Great	-	-	Self-reported; NWS (c)	Self-efficacy 6-items (NWS) (c)	The physical activity intensity of children with ConHD was lower, relative to normative data. Disease severity, self-reported efficacy, overprotection by parents, and negative activity advice from their cardiologist did not explain these differences in physical activity intensity.

= disease specific questionnaire * For their analysis, all authors used the same cohort of Fontan children enrolled in the Paediatric Heart Network Fontan Cross-sectional Study**Congenital heart disease (ConHD)**

AR = arterial redirection, ASO = arterial switch operation, , ES = Eisenmenger syndrome , Fontan = Fontan circulation, HLHS = hypoplastic left heart syndrome, PS = pulmonary stenosis, TCPC= total cavopulmonary connection, TGA = Transposition of the great arteries, TOF = Tetralogy of Fallot, VSD = ventricular septal defect

Exercise capacity

HR= heart rate, VAT= peak oxygen consumption at anaerobic threshold, VO_2max= peak oxygen consumption

Physical activity (PA)

BQ = Baecke Questionnaire, FPACQ = Flemisch Physical Activity Computerizes Questionnaire

Psychosocial functioning

(p) = parent report, (c) = self-report

CBCL = Child Behavior Checklist, CES-D = Centre for Epidemiologic Studies Depression Scale, CHAT = Congenital Heart Adolescent or Teenage questionnaire, CHQ-CF87 = Child Health Questionnaire Child Form, CHQ-PF50 = Child Health Questionnaire Parent Form, IQLC = Inventory for the Assessment of the Quality of Life in Children and Adolescents, KINDL = Children Quality of Life Questionnaire, PedsQL-CF = Paediatric Quality of Life Inventory Child Form, PedsQL-PF = Paediatric Quality of Life Inventory Parent Form, SF-36 = 36 item short form, SH = sleeping habits, TACQOL-CF = TNO-AZL Child Quality of Life Questionnaire, YRBS = Youth Risk Behaviour Surveillance System, YSR = Youth Self Report

Other measurements

BNP = brain natriuretic peptide

the sports-camp or at the follow-up. Unfortunately, the latter two studies used no control groups, so no conclusion regarding causal effects of the sports-camp can be drawn.

DISCUSSION

All studies into children aged 5-18 years reported significant associations between exercise capacity and parent-reported *physical QoL*[2, 15, 17, 21-24]. As to self-reported *physical QoL* in these children, some studies found a positive association with exercise capacity[2, 15, 27, 29]. Remarkably, McCrindle et al.[2] found that higher exercise capacity was associated with both lower self-reported general health and higher parent-reported general health. These contradictory results could be explained by the assessment with different instruments and informants: lower general health was found on a disease specific self-report, and higher general health on a generic instrument for parents. Other studies did not find significant associations between exercise capacity and self-reported physical QoL[16, 17, 24], this might be due to the relative young age of the assessed children.

Regarding *psychosocial* QoL in children under the age of 18, the majority of studies did not find associations between exercise capacity and psychosocial parent-reported and self-reported QoL scales, apart from a few exceptions. Two studies found that higher exercise capacity was associated with higher parent-reported self-esteem[17] or less parent-reported general behavioural problems[2]. In addition, two studies reported that higher exercise capacity was associated with self-reported outcomes: i.e. less stress from illness[16] and less symptom concerns[2].

In summary, in children younger than 18, higher exercise capacity was associated with higher parent-reported physical QoL, but on children's self-reports, no consistent associations were found between exercise capacity and physical QoL scales. Higher exercise capacity was seldom associated with higher self-reported or parent-reported psychosocial QoL.

In studies using mixed samples of adolescents and adults, age-range: 14-73 years, higher exercise capacity was associated with better self-reported physical functioning and general health[25, 26, 29]. Although these studies used a generic QoL instrument (SF-36), rather good correlations between an objective and a self-reported measurement were found (r=0.28 to 0.57). Exercise capacity was not associated with any psychosocial domain of QoL. Considering the broad age-range of these studies, however, we should remain careful to generalize these findings to children and adolescents.

The three studies published so far[13, 16, 17] into the association between exercise capacity and emotional and behavioural problems in children with ConHD, reported contradictory findings. In children with major ConHD[16], no significant associations were found with parent-

reported emotional and behavioural problems, even in the few children who had impaired exercise capacity. Children with moderate ConHD[17] who had lower exercise capacity, showed elevated problem scores. Probably, the remarkable fact that parents of children with major ConHD did not report more emotional and behavioural problems in their children with decreased exercise capacity may be explained by the fact these parents evaluate their children's performance using different norms than healthy children's parents. The last study on this subject[13] found that higher parent-reported exercise capacity was associated with lower parent-reported emotional and behavioural problems in their child. Since both outcomes were parent-reported, they may share variance, and are therefore associated.

Three studies reported on the relation between exercise capacity, physical activity, and *psychosocial functioning*[2, 28, 29]. McCrindle et al.[2] found no association between self-reported physical activity, objective physical activity, and exercise capacity in 7-18-year-olds. In contrast, Muller et al.[28] found that higher exercise capacity was associated with higher objectively assessed physical activity in 8-52-year-olds. These contradictory findings could be explained by different sample sizes and age-ranges, but also by different tests to assess physical activity. McCrindle et al. used a uni-axial accelerometer, whereas Muller et al., used a tri-axial accelerometer. In addition and also in contrast with McCrindle et al., Buys et al.[29] found that higher self-reported physical activity was associated to higher exercise capacity. However, they used a different age-range, 16-40 years, which may explain the difference in this association. In a large cohort of European adolescents from the general population, exercise capacity, measured with a 20-m shuttle run test, correlated with both self-reported moderate-to-vigorous physical activity (MVPA) and objectively measured MVPA, with a uni-axial accelerometer[34] . In addition, self-reported MPVA was moderately correlated with objectively measured MVPA. These findings are partially in line with our findings since they indicate the same association between exercise capacity and physical activity. However, the assessment instruments, i.e. 20-m shuttle run test versus a bicycle test, were different.

Two studies found that higher self-reported physical activity was associated with higher self-reported self-efficacy[18, 19]. These findings should be interpreted with caution, since both physical activity and self-efficacy were self-reported, and thus share variance that may contribute to the association.

To our knowledge, no randomized controlled trials have yet investigated the effect of an exercise program on psychosocial functioning in adolescents with ConHD. Intervention studies on this subject share methodological flaws[30-33]. They were either limited by the use of small groups of patients, by low response rates, the lack of proper control groups, or not using standardized assessment procedures and interventions; e.g. the intervention of Moons et al.[32, 33] consisted of a 3-day multi-sports camp. Therefore, the effectiveness of an exercise program on QoL should be studied in a larger systematic randomized controlled trial.

Conclusions

Exercise capacity was strongly associated with physical domains of QoL, while the association between physical activity and physical domains of QoL was less strong.

Exercise capacity and objectively measured physical activity were almost never associated with psychosocial domains of QoL. Psychosocial QoL was more associated with depressive symptoms. We should be careful, however, drawing firm conclusions; the number of studies using physical activity, as an exercise variable, was relatively small compared to the number of studies assessing exercise capacity.

As to clinical implications, besides measuring medical parameters to describe physical limitations in children with ConHD, it seems useful to include subjective evaluations of these physical limitations. This is important since self-reported depressive symptoms were associated with self-reported physical domains of QoL. Subjective evaluations are best assessed with disease-specific psychological instruments (self- and parent- reported), e.g. health related QoL and depressive symptoms.

The results of the intervention-studies in this review seem to indicate an association between participating in exercise and better physical QoL. A review of exercise program studies in healthy children and adolescents from the general population showed that exercise had a small but significant effect on reducing depression and anxiety scores; due to methodological limitations, drawing firm conclusions was not possible[35]. Our review also indicates an association between self-reported physical limitations and depressive symptoms. This underlines the importance and clinical relevance of the medical recommendation of sports participation for CONHD children[9]. This clinical implication could be made stronger if there were results of a randomized controlled trial into the cardiovascular and psychosocial effects of an exercise program in children with ConHD.

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Chapter 3

Aerobic exercise influences quality of life of children and youngsters with congenital heart disease; a randomized controlled trial

Karolijn Dulfer, Nienke Duppen, Irene M. Kuipers, Michiel Schokking, Ron T. van Domburg, Frank C. Verhulst, Willem A. Helbing, Elisabeth M.W.J. Utens

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ABSTRACT

Purpose

To evaluate effects of an exercise program on health related quality of life (HRQoL) in children and adolescents with Tetralogy of Fallot (ToF) or a Fontan circulation.

Methods

Stratified, randomized, controlled intervention study conducted in 5 participating centres of paediatric cardiology in the Netherlands. In total, 93 patients, aged 10 – 25, with surgical repair for tetralogy of Fallot or with a Fontan circulation for single-ventricle physiology were included. They were randomly allocated with a ratio of 2:1 to: a) a 12-week period with an exercise program for 3 times per week or b) to a control group. Randomization was stratified by age, gender, and cardiac diagnosis. At baseline and follow-up after 12 weeks, all participants completed web-based age-appropriate HRQoL questionnaires. Primary analyses involved change in HRQoL during follow-up. Secondary analyses concerned influence of cardiac diagnosis and comparison with normative data.

Results

Respectively 48 (86%) and 32 (86%) patients in the exercise group and control group completed all questionnaires at baseline and follow-up. Compared with the control group, children, aged 10 – 15, in the exercise group improved significantly on self-reported cognitive functioning, $p<.05$, $r = .30$, and parent-reported social functioning, $p <.05$, $r = 0.30$. Youngsters aged 16 to 25 did not change their HRQoL. Cardiac diagnosis had no influence on pre-post changes. Children and youngster in this study reported comparable or better HRQoL than norm groups.

Conclusions

Participation in an exercise program improved HRQoL of children with ToF or a Fontan circulation, especially in those with low baseline HRQoL.

INTRODUCTION

Nowadays, at least 85% of children born with congenital heart disease (ConHD) survive into adulthood[1]. These children may experience long-term physical morbidity. Compared with healthy peers, adolescents with severe ConHD have reduced exercise capacity[2, 3].

Although children and adolescents with ConHD are recommended to participate in physical activity, as stated in the guidelines from the European Society of Cardiology[4], they do not perform the same amount of dynamic physical activity compared with healthy peers[5]. Reduced exercise capacity has been associated with reduced health related quality of life (HRQoL) in children with ConHD[6]. Adolescents with mild or severe ConHD and reduced exercise capacity, reported lower overall HRQoL than their healthy peers. Those with severe ConHD, i.e. Fontan circulation, reported a worse HRQoL than those with mild ConHD[7].

The few studies conducted into an exercise program showed promising results regarding improving exercise capacity and physical activity in adolescents with ConHD[8, 9]. The studies, with small samples, showed that peak oxygen consumption improved, as did workload[10], exercise time[10], and daily physical activity[11]. However, little is known about the impact of an exercise program on HRQoL in these adolescents.

In adults with ConHD, HRQoL improved after an exercise program[12]. Until now, three studies, using small samples, have examined the effect of a 3-day sports camp[13, 14], or a 12-week exercise program[15] on self-perceived health status in adolescents with ConHD . To our knowledge, no *randomized controlled trial* in adolescents with ConHD has been done to examine the effect of an exercise program on HRQoL.

The present prospective, multicentre study is a randomized controlled trial into the effect of a standardized exercise program on HRQoL in a relatively large cohort of patients, aged 10 to 25, with either surgical repair for ToF or a Fontan circulation. Two-third of the ToF and Fontan patients included were randomized to an aerobic exercise program; the remaining one-third served as controls. We hypothesized that an exercise program would improve HRQoL in these patients.

The present study's aim was to answer the research questions:

1. What is the effect of a 12-week exercise program versus a control group in patients aged 10-25 with ToF or Fontan circulation, on their health related quality of life?
2. What is the influence of cardiac diagnosis on the HRQoL-effects of the exercise program?
3. What is the level of health related quality of life, at baseline and post assessment, in patients who participated in the exercise program and in the control group, compared to that of same aged peers from the general population?

METHODS

This randomized controlled trial is designed according to the CONSORT guidelines[16].

Inclusion/exclusion

Included were patients, aged 12 to 20, who underwent cardiac surgery before the age of 2 years for ToF, and patients, aged 10 to 25, who underwent surgery for single-ventricle physiology (intra-cardiac or extra-cardiac tunnel type of Fontan-completion, at least 2 stages) before the age of 6 years. Patients were treated at one of the 5 participating centres of paediatric cardiology in the Netherlands: Academic Medical Centre Amsterdam, Erasmus Medical Centre Rotterdam, Leiden University Medical Centre, University Medical Centre Radboud, and University Medical Centre Utrecht.

Excluded were patients with: contra-indications for exercise, mental retardation, standard contra-indications for magnetic resonance imaging (MRI), or a ventricular outflow obstruction (peak Doppler gradient > 60 mm Hg).

Randomization

After informed consent had been obtained, patients received an anonymous study code and were invited for medical and psychological *baseline* assessments. Thereafter, a 'blind' independent researcher allocated the patients to the exercise program or the control group (ratio 2:1) according to restricted randomization. We formed balanced groups through stratification by age group, gender, and ConHD, together with fixed block sizes of 3. In addition, the overall study sample size[93] is a multiple of the block size[3], which guaranteed that the number of participants assigned to each treatment group would be equal. Within each fixed block, the first and second patients in the stratification-group (e.g. age-group 10-12, boys, Fontan) were randomized through envelopes. The randomization of the third patient within the randomization block depended on the previous two randomizations.

Intervention

The standardized exercise program consisted of 3 training sessions of 1 hour per week, during a 12-week period. Patients who already participated in sports activities were instructed to continue these activities and participate in the exercise program 2 times a week. The exercise program consisted of 10 minutes warming-up, 40 minutes aerobic dynamic cardiovascular training, and 10 minutes cooling down. Cardiovascular training included brisk walking/jogging/running/bicycle exercises, and dynamic play. Participants were given a heart rate monitor and were instructed to perform their exercises within the given heart range (resting heart rate plus 60-70 % of the heart rate reserve, for details see Duppen et al. 2013[8] and

Tikkanen et al. 2012[9]). This range was determined by the ergometer-test performed at the baseline assessment. They were not allowed to train above the prescribed range.

Since training intensity level was monitored and adjusted according to a pre-determined heart rate range, workload was directly adjusted to heart rate levels. This meant that improvements were directly reflected in individualized workloads. The intensity range was programmed in their heart rate monitor; an alarm informed them when they did not adhere to this range.

The program was performed group-wise, under supervision of a trained and licensed physiotherapist in local centres throughout the Netherlands. The same researcher (ND) visited all participating physiotherapists prior to the start of the program and visited them thereafter when needed, to ensure standardized implementation of the exercise program. The control group continued their normal daily live and were invited for a baseline and a follow-up medical and psychological assessment.

Assessment procedure

The ethics-committee review boards of all 5 medical centres approved the research protocol. All eligible patients and their parents were approached uniformly through a patient-information letter and completed the same psychological instruments at 2 points in time. The baseline psychological assessment, a *web-based* questionnaire and a semi-structured interview by phone, took place no longer than 2 months before the start of the exercise program, and 1-3 days before the baseline cardiac assessment in the hospital. The second psychological assessment was performed no later than one month after completion of the exercise program, and no more than 2 weeks after the second cardiac assessment in the medical centre. Assessments for control groups were performed at comparable timepoints.

Semi-structured interview

A semi-structured interview[17] was completed by phone. Separate questions were included for children, aged 10 – 15, adolescents/young adults, aged 16 – 25, and for parents of children/adolescents, aged 10 – 18. In these interviews biographical data, such as household composition, educational level, social participation, professional mental health care consumption, and perceived body image were assessed.

Socioeconomic status of parents was divided into low, middle, and high occupational level[18].

Web-based questionnaire

The web-based questionnaire consisted of a child-version and a parent-version. It encompassed the following internationally well-known, age-appropriate, HRQoL assessment-instruments with good psychometric properties (reliability and validity).

Generic instruments for children aged 10-15

The TNO/AZL Child Quality of Life Questionnaire (TACQOL) Child Form (CF) and Parent Form (PF) were used to assess generic aspects of HRQoL; see table 2 for subscales[19]. These questionnaires assess the occurrence of functional problems, and if such problems occur, the subsequent emotional reactions to these problems. Satisfactory psychometric properties (subscale Cronbach's α ranged from 0.73 to .082) of these instruments have been described by Verrips et al.[20].

The Linear analogue scale (LAS) measured self-perceived QoL (vertical line; 0 = worst, 100= best imaginable QoL). The LAS has proven to be valid and reliable (Cronbach's α = 0.65) for the ConHD population[13].

Generic and cardiac-specific instruments for patients aged 16 and older

The SF-36 Health Survey (SF-36), a generic instrument, was used to assess subjective health status (table 3)[21]. Good reliability (mean Cronbach's α = 0.84) and validity has been reported for the Dutch version[22].

The Congenital Heart Disease-TNO/AZL Adult Quality of Life (CONHD-TAAQOL) assessed cardiac-specific aspects of HRQoL of youngsters with ConHD (table 4). Tests of its psychometric properties showed satisfactory results; Cronbach's α ranges from 0.77 to 0.82[1].

The Linear analogue scale (LAS) measured self-perceived QoL (see above).

Norm groups

For the ***TACQOL-CF***, the norm group consisted of 593 girls and 660 boys (n=1253)[19] . For the TACQOL-PF no normative data were available.
The ***SF-36*** norm sample consisted of 1742 persons; 56 % men, age range: 16-40 years[22].
For the disease-specific ***CONHD-TAAQOL***, no normative data were available.
The ***LAS*** norm sample contained 600 participants aged 14 to 18.

Statistical analyses

Statistical analyses were based on the intention-to-treat principle. Because of small sample sizes and skewed distributions, exercise group changes *versus* control group changes were compared with Mann-Whitney tests ($p<.05$), also for diagnostic groups separately. Repeated measurements *within* the exercise group and control group were analysed with Wilcoxon Signed Ranks Tests. Data are presented as median and inter quartile range (IQR). The effect size (*r)* for every result is calculated by the z-score divided by the square root of the number of observations.

Then data were split, based on baseline HRQoL tertiles, into 'low' (=1st tertile), and 'high' (=2nd and 3rd tertiles) and pre-post changes in the exercise group and control group were analysed for baseline HRQoL groups separately. Because many children and parents obtained highest possible HRQoL scores, we also analysed whether children and their parents

changed their maximal scoring after the exercise program and control period with McNemar tests.

Comparison with normative groups was calculated using Students' t tests (mean and standard deviations). Statistics were conducted using SPSS version 20.0 (IBM Corp., Armonk, NY).

RESULTS

Baseline characteristics

362 Eligible patients were contacted, of whom 93 (26%) finally participated, see figure 1 for flowchart. Two patients who were assessed at baseline refused to participate in the rest of the study. Therefore, the final sample included 91 participants, median age: 15.4 years, 64/91 male, 47/91 ToF, 44/91 Fontan. Patients were recruited and followed-up between January

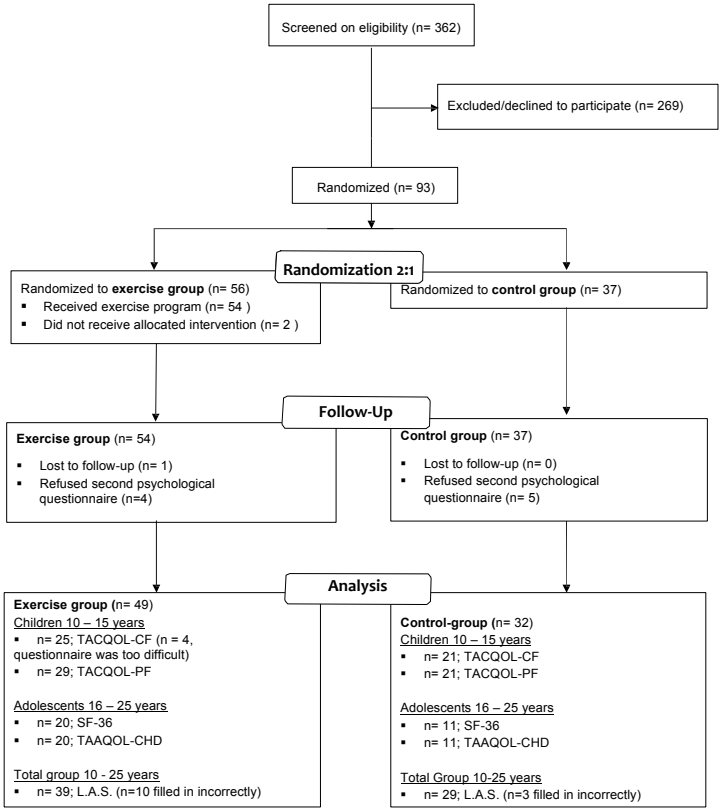

Figure 1: Enrollment in study

2010 and August 2012. No differences were found as to baseline characteristics between the exercise group and the control group; see table 1.

Table 1: baseline demographic characteristics, cardio-respiratory fitness, and participation in sports activities

	Exercise group (n=54)	Control group (n=37)	P value
Demographic status			
Age in years	15.2 (12.6-17.6)	15.4 (13.0-17.6)	0.77
Male	39 (72.2)	26 (70.3)	0.64
Congenital heart disease			0.70
Fontan	27 (50.0)	17 (45.9)	
Age at Fontan completion	3.0 (2.5–5.0)	3.0 (2.5–3.9)	0.66
Tetralogy of Fallot (ToF)	27 (50.0)	20 (54.1)	
Age at ToF operation	0.5 (0.4–1.1)	0.7 (0.5–0.9)	0.61
Social economic status			0.46
Low (1)	5 (9.3)	4 (10.8)	
Middle (2)	16 (29.6)	15 (40.5)	
High (3)	27 (50.0)	14 (37.8)	
Missing	6 (11.1)	4 (10.8)	
Cardio-respiratory fitness			
*PeakVO_2 (% predicted)**	82.4 (17.0)	81.7 (20.0)	0.88
Peak load in Watt	143.6 (54.6)	147.0 (46.2)	0.76
Peak heart rate (bpm)	170.8 (20.4)	176.5 (18.6)	0.18
VE/VCO_2 slope	28.7 (5.3)	29.9 (6.8)	0.36
Participation in sports activities			0.35
Never	9(17)	8(22)	
1-4 hpw	33(61)	17(46)	
>5 hpw	12(22)	12(32)	

Demographic status and participation in sports activities: data are presented as number (percentage), age is presented as median (IQR).

Cardio-respiratory fitness: data are presented as mean (standard deviation).

* n = 11 missing values due to unsuccessful cardiopulmonary exercise test (respiratory exchange ratio (RER) < 1.0.)

Hpw = hours per week, bpm = beats per minute.

Exercise program adherence

Overall, 56 patients were randomized to the exercise group, of which 53 were followed-up after 3 months (see Figure 1). Of these patients in the exercise group, 37 already participated in sports activities in their daily lives. Median adherence to the exercise program was 89% (IQR = 79 – 100). According to a random sample of heart rate monitor data, all exercise-

patients heart rate ranges during the exercise program were within the advised heart rate range.

Effects of an exercise program on quality of life

Children aged 10-15 years; TACQOL

Of the 32 children in the exercise program group and 22 children in the control group, respectively 25 and 21 children completed the TACQOL-CF (see table 2). Comparing pre-post change in the exercise group versus the control group, children in the exercise group improved more on cognitive functioning $z = -1.99$, $p<.05$, $r = .30$ than control children.

Considering pre-post changes *within each group,* children in the exercise group themselves reported better motor functioning after the sports-intervention than before $z = -2.11$, $p < .05$, $r = .30$. Control children themselves scored higher, i.e. more favourable, on global negative functioning from pre-to post assessment, $z = -1.98$, $p < .05$, $r = .31$.

29 Parents in the exercise group and 21 parents in the control group completed the TACQOL-PF. Comparing pre-post changes, parents of children in the exercise group reported improved social functioning whereas parents of control children did not, $z = -2.07$, $p < .05$, $r = 0.30$.

Within both groups, parents reported improvements ($p<0.01$, *r-range:* 0.44 - 0.53) on pain and physical symptoms, motor functioning, and cognitive functioning (table 2). Parents in the exercise group also reported improvements on social functioning ($p=0.006$. $r = 0.36$).

Since the exercise program showed few significant effects on TACQOL-CF scores, further statistical analyses were performed for children who had low HRQoL scores at baseline. Children in the exercise group with low baseline scores on motor functioning and cognitive functioning, showed significant improvements on these scales, $z = -2.54$, $p < .05$, $r = .57$ and $z = -2.11$, $p < .05$, $r = .50$; see figure 2. They also seem to improve ($p= .068$, $r = .43$) on pain and physical symptoms. However, children in the control group, with 'low' baseline HRQoL, did not improve on these scales, they only improved on negative emotional functioning ($p< .05$, $z = .47$).

As to best possible scores, children in both groups did not obtain a higher number of maximal HRQoL scores from baseline to follow-up. On the other hand, parents in the exercise group reported a higher number of maximal scores for pain and physical symptoms ($p=.01$), motor functioning ($p<.01$), cognitive functioning ($p<.01$), and social functioning ($p<.02$) from pre- to post-assessment, whereas parents in the control group did not.

Table 2: Quality of Life questionnaire for children aged 10-15 years

TNO/AZL Child Quality of Life Questionnaire - Child Form (TACQOL-CF)						
	Exercise group (n=25)		**Control group (n=21)**		p value Δexercise vs Δcontrol	**Normative data Child Form**
Scales	Baseline	Follow-up	Baseline	Follow-up		
Pain and physical symptoms	25.0 (21.5-28.0)	26.0 (22.5-30.5)[b]	24.0 (19.5-27.0)	23.0 (20.0-29.0)	0.21	24.0 (20.0-28.0)
Motor functioning	30.0 (26.5-30.5)	30.0 (29.0-31.5)[a]	28.0 (26.0-31.5)	30.0 (26.5-32.0)	0.51	31.0 (29.0-32.0)
Cognitive functioning	27.0 (23.8-30.0)	29.0 (26.3-30.8)	30.0 (24.0-32.0)	29.0 (23.0-31.8)	0.05	28.0 (25.0-31.0)
Social functioning	32.0 (30.0-32.0)	32.0 (28.0-32.0)	32.0 (30.5-32.0)	32.0 (32.0-32.0)	0.45	32.0 (32.0-32.0)
Positive emotional functioning	15.0 (13.5-16.0)[b]	15.0 (11.5-16.0)	15.0 (11.5-16.0)	15.0 (12.3-16.0)	0.39	14.0 (11.0-15.0)
Negative emotional functioning	13.0 (10.0-16.0)	14.0 (12.0-16.0)[b]	13.0 (11.3-14.0)	14.0 (13.0-15.8)[a,b]	0.34	12.0 (10.0-14.0)
TNO/AZL Child Quality of Life Questionnaire - Parent Form (TACQOL-PF)						
	Exercise group (n=29)		**Control group (n=21)**		p value Δexercise vs Δcontrol	
Scales	Baseline	Follow-up	Baseline	Follow-up		
Pain and physical symptoms	28.0 (23.0-29.0)	30.0 (27.5-32.0)[a]	27.0 (24.0-28.5)	30.0 (27.5-31.0)[a]	0.76	
Motor functioning	28.0 (26.5-30.5)	32.0 (31.0-32.0)[a]	30.0 (27.0-32.0)	32.0 (30.0-32.0)[a]	0.21	
Cognitive functioning	27.0 (22.5-30.0)	32.0 (29.0-32.0)[a]	29.0 (24.0-31.0)	32.0 (30.0-32.0)[a]	0.73	
Social functioning	32.0 (28.0-32.0)	32.0 (32.0-32.0)[a]	32.0 (32.0-32.0)	32.0 (32.0-32.0)	0.04	
Positive emotional functioning	16.0 (13.5-16.0)	15.0 (14.0-16.0)	15.0 (12.8-16.0)	15.5 (13.8-16.0)	0.39	
Negative emotional functioning	13.0 (10.0-13.0)	13.0 (10.0-14.0)	11.0 (9.0-13.0)	13.0 (12.0-14.0)[a]	0.15	

Data are presented as median (IQR), Δexercise indicates change in the exercise group during follow-up, and Δcontrol indicates change in the control group during follow-up.

A higher score indicates a better quality of life.

a) Significant different from pre-to-post using the Wilcoxon Signed Ranks Test; $p<0.05$

b) Significant different from reference; $p<0.05$

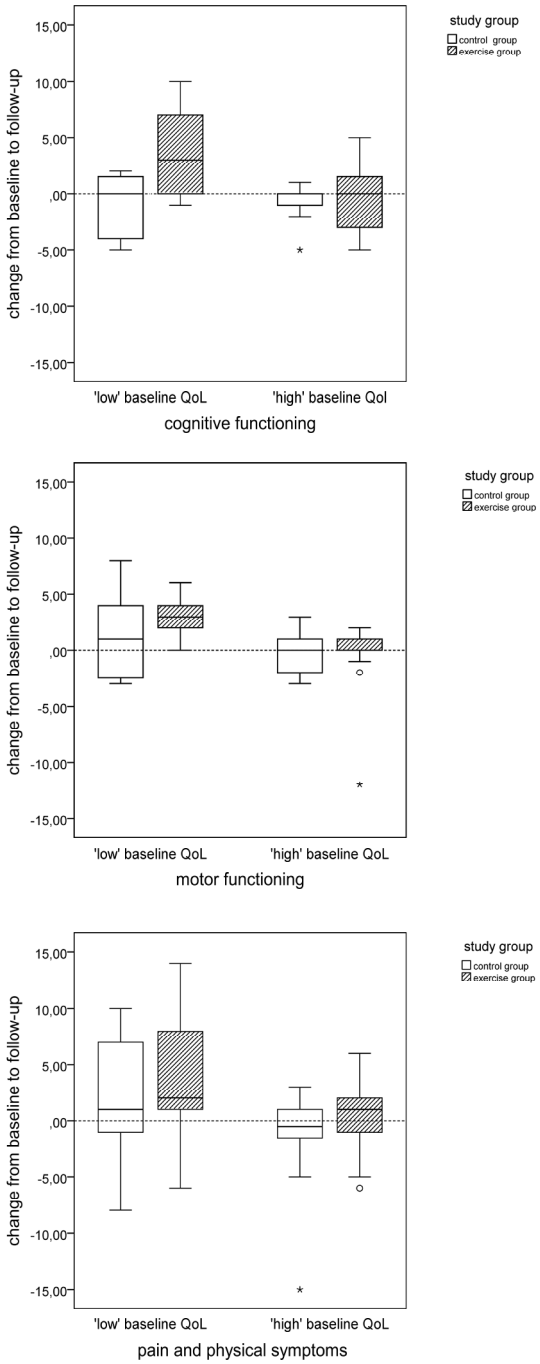

Figure 2: Differences in pre-post changes in quality of life (QoL) between patients with low baseline QoL and high baseline QoL

Patients aged 16 - 25 years; SF-36

No significant differences in pre-post changes on the SF-36 were found between the exercise group and control group. Such pre-post changes were neither found *within* each group; table 3. Many patients obtained best possible SF-36 scores.

Patients aged 16-25 years; CONHD-TAAQOL

Patients in the exercise group and the control group did not show pre-post changes on the *symptoms* and the *worries* scale (table 3). Considering impact of cardiological surveillance, adolescents reported lower scores after the exercise program than they did before z =-3.03, $p < .01$, $r = .54$. Adolescents in the control group did not change on impact of cardiological surveillance. The median difference between the pre-post changes in the exercise group and the control group was 5.7 p=0.07.

Total group 10 - 25 years

Changes in LAS scores did not differ between the exercise group and control group. No significant changes were found within each group.

Cardiac diagnosis and comparison with normative data

Cardiac diagnosis, Fontan versus Fallot, did not influence the effect of an exercise program on the generic TACQOL (child-form nor parent-form), SF-36 scales, disease-specific CONHD-TAAQOL, nor on the LAS.

Children aged 10-15 years; TACQOL

At baseline, self-reports of Fontan children did not differ from ToF children on any of the TACQOL-CF scales. Parents of Fontan children reported worse motor functioning than parents of ToF children, z=-2.55, p <.02, r = .40. No further differences between diagnostic groups were found on parent-scales.

Comparing baseline with normative data, Fontan children reported poorer motor functioning (t(25)=-2,93, p<.01) and less negative emotions (t(25)=2.56, p = .02), whereas ToF children reported more positive emotions (t(18)=3.11, p<.01).

Patients aged 16 - 25 years; Short-form 36

At baseline, Fontan patients reported worse physical functioning, z = -2.14, $p < .05$, r = .38 and lower general health, z = -2.74, p <.01, r =.49 than ToF patients (table 3).

Compared with normative data, Fontan patients and ToF patients reported less bodily pain (both $p < .01$), better social functioning (both p <.01), and less role limitations due to emo-

Table 3: Quality of Life questionnaires for adolescents aged 16-25

	Fontan (n = 9)	Tetralogy of Fallot (n=22)	Normative data (16-40) Mean (sd)	Exercise group (n=20)		Control group (n=11)		p value Δexercise vs Δcontrol
	Baseline	Baseline		Baseline	Follow-up	Baseline	Follow-up	
Short-Form 36 (SF-36)								
Physical functioning	90.0 (65.0-95.0) [b]	97.5 (90.0-100.0) [b]	93.1 (11.8)	97.5 (80.0-100.0)	97.5 (86.3-100.0)	95.0 (90.0-100.0)	95.0 (90.0-100.0)	0.71
Bodily pain	100.00 (84.7-100.0) [c]	100.0 (89.8-100.0) [c]	80.9 (19.4)	100.0 (89.8-100.0) c	100.0 (89.8-100.0) [c]	100.00 (89.8-100.0)[d]	100.0 (79.6-100.0) [d]	0.96
General health	45.0 (40.0-70.0) [b, d]	75.0 (63.8-91.3) [b]	78.2 (17.3)	75.0(52.5-88.8)	70.0 (50.0-85.0) [d]	60.0 (60.0-80.0)	67.5 (56.3-78.8)	0.94
Vitality	75.0 (62.5-80.0)	75.0 (63.8-85.0)	70.7 (16.4)	75.0 (61.3-85.0)	70.00 (61.3-83.8)	75.0 (65.0-85.0)	70.0 (60.0-80.0)	0.56
Role limitations due to physical limitations	100.0 (87.5-100.0)	100.0 (100.0-100.0)	86.4 (27.6)	100.00 (100.0-100.0)[d]	100.0 (100.0-100.0) [c]	100.0 (100.0-100.0)[c]	100.0 (75.0-100.0)	0.16
Social functioning	100.0 (93.8-100.0) [c]	100.0 (100.0-100.0) [c]	87.8 (19.1)	100.0 (100.0-100.0) [c]	100.0 (87.5-100.0)	100.0 (87.5-100.0)	100.0 (100.0-100.0)[c]	0.09
Role limitations due to emotional problems	100.0 (100.0-100.0) [d]	100.0 (100.0-100.0)	85.4 (30.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0) [c]	100.0 (100.0-100.0)[c]	100.0 (100.0-100.0)	0.72
Mental Health	80.0 (74.0-92.0)	88.0 (75.0-96.0) [d]	78.7 (15.2)	86.0 (76.0-95.0) [d]	86.0 (74.0-95.0)	84.0 (68.0-96.0)	80.0 (76.0-88.0)	0.65
The Congenital Heart Disease-TNO/AZL Adult Quality of Life (CONHD-TAAQOL)								
Symptoms	93.3 (88.9-97.8)	97.8 (92.8-100.0)		96.7 (91.1-100.0)	96.7 (90.0-100.0)	95.6 (91.1-97.8)	97.8 (95.6-100.0)	0.16
Impact Cardiological Surveillance*	85.7 (75.0-89.3) [b]	91.4 (85.7-97.9) [b]		91.4 (86.4-96.4) [a]	85.7 (80.7-88.6) [a]	85.7 (76.7-90.0)	85.7 (82.9-88.6)	0.07
Worries	90.0 (82.0-95.0) [b]	100.0 (90.0-100.0) [b]		99.0 (91.0-100.0)	98.0 (89.0-100.0)	90.0 (84.0-100.0)	94.0 (72.0-100.0)	0.67

Data are presented as median (inter quartile range), only reference data are presented as mean (standard deviation), a higher score indicates a better quality of life.

a) significant different from pre-to-post using the Wilcoxon Signed Ranks Test; $p<0.05$

b) significant differences between Fontan and tetralogy of Fallot adolescents using the Mann-Whitney Test ($p<.05$)

c) significant different from reference group $p<0.01$

d) significant different from reference group $p<0.05$

* Comprise items like: In the last twelve months, have you had an ultrasound heart scan (MRI), when answered with yes, the subjective evaluation is assessed: how much did that bother you?

tional problems (both p <.05) at baseline. Patients with ToF also reported less role limitations due to physical symptoms (p <.05) and better mental health (p <.05). Furthermore, Fontan patients reported lower general health (p <.05), whereas ToF patients' general health was comparable to normal (table 3).

Patients 16 - 25 years; CONHD-TAAQOL

At baseline, Fontan adolescents reported more impact of cardiological surveillance, z = -2.07, p <.05, r = .37 and more worries, z = -2.15, p <.05, r = 0.39 than ToF adolescents, see table 3.

Total group 10 - 25 years; LAS

At baseline, Fontan children and adolescents reported comparable LAS scores (M*dn* = 80.0, IQR = 73.8 - 90.0) as ToF children and adolescents (M*dn* = 80.0, IQR = 70.0 - 85.0).

Exercise group and control group versus normative data

Children aged 10-15 years; TACQOL

At baseline, children in the exercise group reported more positive emotions (p <.05) than children from the general population (table 2). At follow-up, children in both study-groups reported less negative emotions than healthy peers (both p <.05). Moreover, children in the exercise group reported less pain and physical symptoms *(p* <.05).

Patients aged 16 - 25 years; SF-36

Comparing baseline with normative data, patients in the exercise group and control group reported less bodily pain *(p<.01 and p<.05),* less role limitations due to physical limitations *(p<.05 and p<.01*), and less role limitations due to emotional problems (*both p<.01*) (table 3). At baseline, adolescents in the exercise group also reported better social functioning (*p*<.01) and mental health (*p<.05*) than peers from the general population.

On post-assessment, patients in the exercise group reported sustained higher, more favourable scores for bodily pain (*p<.01*), role limitations due to physical limitations (p<.01), as well to emotional problems (*p*<.01) compared with normative data. In contrast, they reported lower general health (*p*<.05). Patients in the control group had sustained higher scores on bodily pain *(p*<.05).

Adolescents aged 14 - 18 years; LAS

At baseline, adolescents in the control group reported significantly better QoL at baseline than normative data, LAS means: 84.7 versus 76.7, $t(13) = 2.91$, $p = 0.012$. Adolescents in the exercise group did not report significantly better QoL at baseline compared with normative data: LAS means: 79.1 versus 76.7.

DISCUSSION

This study shows that children with ConHD between 10 and 15 years old, who participated in a standardized exercise program, improved on self-reported cognitive functioning. This is particularly true for those with low baseline HRQoL scores. In this subgroup, improvements were noted on both cognitive and motor functioning and there was a trend towards improvements on pain and physical symptoms. Children in the control group with low baseline HRQoL scores did not improve on these scales.

According to parent-reports, children who participated in an exercise program improved on social functioning. However, almost all parents in both groups reported highest possible scores on social functioning; due to this ceiling effect of the questionnaire, this result is not very informative.

Analyses within groups showed that parents in both the exercise group and control group reported improvements on pain and physical symptoms, motor functioning and cognitive functioning. At follow-up, parents from both groups obtained more best possible scores for motor functioning and cognitive functioning. Possibly, the extensive examination, both medical and psychological, may have given parents a feeling of more safety and results may point towards a placebo effect.

The exercise program did not change QoL of adolescents and young adults, as shown by the generic SF-36 and LAS. This can be due to the fact that most adolescents had best possible scores at baseline. Beside this ceiling effect at baseline, they also reported better QoL compared with normative data. Presumably, these generic instruments are not sensitive enough to detect QoL changes in this patient population[1]. On the other hand, the ceiling effect was also noted on the disease-specific CONHD-TAAQOL. Higher scores might also be caused by selection bias; patients participated voluntarily to this study. These motivated patients have reported perhaps higher QoL scores than patients who did not participate.

An exception was that adolescents in the exercise group reported more impact from cardiac surveillance at follow-up. These adolescents participated in an intensive 3-month program; therefore they may have perceived their cardiac surveillance at follow-up more as a burden, whereas adolescents in the control group did not.

As to cardiac diagnosis, ToF versus Fontan, we did not find any influence of diagnosis on HRQoL changes after the exercise program. Latal et al.[23] reviewed studies into QoL in children and adolescents with ConHD. They also found that cardiac diagnosis did not relate to QoL in a heterogeneous diagnostic sample. On the other hand, they found lower QoL scores in those children and adolescents with more complex malformations, such as single ventricle anatomy palliated with a Fontan operation. In line, adolescents/young adults with a

Fontan circulation in our sample also reported lower baseline SF-36 physical functioning and general health compared with those with ToF. However, adolescents/young adults with a Fontan circulation in our sample did not report greater HRQoL-changes in these or any other domains than adolescents/young adults with ToF.

To our knowledge, so far only three small studies into the influence of an exercise program on health status in ConHD children have been done[14, 15, 24]. The only intervention study[15] that used a similar standardized 12-week exercise program, did not find the improvements in parent-reported HRQoL that we found. Rhodes et al.[15] only showed non-significant improvements on all self-reported QoL domains after rehabilitation. They assessed QoL 1 year after the exercise program with a health status questionnaire. Health status, however, is another concept than health related quality of life, which we assessed[25]. In addition, their control group consisted of volunteers, who could not participate in the exercise program for geographical or social constraints. The difference with our findings may also relate to their smaller sample size. Finally, Rhodes et al. only included those children and adolescents with a peakVO2 of 80% predicted or less. Mean baseline peakVO_2 percent predicted was 64.7% in their control group and 59.6% in their exercise group. In our sample, see Table 1, baseline mean peakVO_2 percent predicted was 82.4 % in the exercise group, and 81.7 % in the control group[15].

Two other intervention studies used a 3-day multi sports camp as intervention[14, 24] and reported improvements on several quality of life domains. However, findings are difficult to compare since the content of their intervention was very different, no control group was used, and their recall time frame of 3 days might have influenced their results.

Strengths and limitations

This is the first randomized controlled trial in this field with a standardized 12-week exercise program, an adequate control group, and multi-informant HRQoL instruments. We found improvements on two domains of HRQoL, in one age group. Possibly, if assessments would have been done with a more disease-specific questionnaire, instead of a generic one, and in a larger sample, we would have found better results.

As to limitations, though our sample size is larger than in the few previous studies, it is relatively small. Due to age-appropriate HRQoL questionnaires, our sample had to be divided into two groups, 10 – 15 years and 16 – 25 years. Therefore, sub-samples sizes were relatively small which may be associated with an increased type 2 error. Besides, a larger sample would have allowed us to investigate the differential impact of gender on the effects of an exercise program.

Regarding our design, those participants in the exercise group who already participated in sports activities themselves, were asked to participate in the exercise program for 2 sessions per week, in addition they were asked to monitor their own sports activities with a

heart rate monitor. Those participants, who did not already participate in sports activities themselves, were asked to participate 3 times. On the other hand, participants in the control group were asked to continue their own regular daily activities (including sports activities). Although we are aware of the interference with our 'controlled' design, in our opinion it would have been unethical to ask participants to discontinue their own sports activities.

Finally, a second, longer-term follow-up might have unravelled any sleeper-effects; i.e. long-term effects of interventions. Unfortunately, a second follow-up was not feasible.

Conclusion

This exercise program improved self-reported cognitive functioning and parent-reported social functioning in children aged 10 to 15. In contrast, this exercise program did not improve the QoL of patients aged 16-25 years. This might be explained by their high self-reported baseline QoL. Another explanation is that a more age-appropriate sports-intervention, with more focus on obtaining autonomy and belonging to a peer-group, involving more 'normal' sports-participation with healthy peers, might have given better results.

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Chapter 4

Effects of an exercise program on emotional and behavioural problems in adolescents with tetralogy of Fallot or a Fontan circulation; A randomized controlled trial

Karolijn Dulfer, Nienke Duppen, Nico A. Blom, Ron T. van Domburg, Willem A. Helbing, Frank C. Verhulst, Elisabeth M.W.J. Utens

In press as Letter to the Editor (see Appendix 1)

ABSTRACT

Objectives

To evaluate effects of a standardized exercise program on emotional and behavioural problems in adolescents with tetralogy of Fallot (ToF) or a Fontan circulation.

Methods

Stratified randomized, controlled, intervention-study, conducted in 5 tertiary centres of paediatric cardiology in the Netherlands. 71 adolescents aged 10-17, with surgical repair for ToF or with a Fontan circulation, were included. They were randomly allocated to: a) a 12-week period with an exercise program for 3 times per week or b) to a control group, with a ratio of 2:1. Randomization was stratified by age, gender, and type of ConHD. At baseline and after 12 weeks, all participants completed online psychological questionnaires. Primary analysis involved change in emotional and behavioural problems during follow-up. Secondary analyses concerned influence of age, gender, and cardiac diagnosis, and comparison with normative data.

Results

Overall, a standardized exercise program had no effect on emotional and behavioural problems. From pre-to post assessment, adolescents within the exercise group reported a pre-post decrease in anxiety for sports. Adolescents within the control group reported improvements on internalizing problems. As to gender and age, girls in the control group, especially those who were older, improved on internalizing problems. Girls in the exercise group did not. Cardiac diagnosis did not influence the results. Compared with normative data at follow-up, adolescents and their parents obtained on almost all scales comparable or better scores.

Conclusions

A standardized exercise program for 3 months did not change emotional and behavioural problems. Overall, parent-reported and self-reported emotional and behavioural problems were lower than or comparable to normative data.

INTRODUCTION

Over the last decades, improvements in diagnostic techniques and pre-, peri-, and post-operative care have resulted in better cardiac outcomes in children with congenital heart disease (ConHD)[1]. Despite these cardiac improvements, children and adolescents with ConHD remain at risk for elevated levels of emotional and behavioural problems, compared with normative data[2]. In a meta-analysis, Karsdorp et al. showed that adolescents with ConHD reported more internalizing and externalizing problems than healthy peers[3].

A review of studies in healthy children and adolescents from community samples showed that physical activity improved mental health, reduced depressive symptoms, and enhanced self-esteem[4]. And a longitudinal study in healthy adolescents showed that those who met recommended levels of physical activity had fewer emotional problems at 1-year follow-up[5].

Youngsters with ConHD are encouraged to participate in an exercise program since it improves fitness and physical activity in ConHD youngsters[6, 7]. However, little is known about the effect of an exercise program on emotional and behavioural functioning of these adolescents. As far as we know, only three non-randomized studies have been done in this field[8-10]. Unfortunately, these studies share methodological problems: small sample sizes, low response rates, no control groups, or no standardized assessment procedures. Moreover, the interventions applied in these studies differed: a) 2 weeks in a rehabilitation centre or 5 months near their home[8], b) a 3 days sports-camp[9], and c) a 12 week exercise program[10]. Overall, these studies found positive results; less internalizing problems and improvements on emotional, behavioural, and physical functioning, as reported by parents. However, on self-reports no significant effects were found.

The present study is part of a multi-centre, prospective, randomized controlled, intervention study into the effects of a standardized exercise program in a large cohort of youngsters, aged 10-25 years, with either tetralogy of Fallot (ToF) or a Fontan circulation. Two-third of the youngster was randomized to a standardized exercise program; the remaining one-third served as controls.

We hypothesized that an exercise program would improve levels of emotional and behavioural problems in these adolescents.

The present study's aim is to answer the following research questions:

1. What is the effect of a 12-week exercise program in adolescents aged 10-17 with ToF or Fontan circulation on the level of emotional and behavioural problems, compared with a control group from pre- to post assessment?
2. What is the level of emotional and behavioural problems in adolescents in the exercise group and in the control group at follow-up compared with normative data?

3. What is the influence of age, gender, and cardiac diagnosis on the effect of the exercise program on emotional and behavioural problems?

METHODS

This randomized controlled trial is designed according to the CONSORT guidelines[11].

Inclusion/exclusion

Included were adolescents aged 12 to 17, who underwent cardiac surgery before the age of 2 for ToF, and adolescents aged 10 to 17, who underwent surgery for single-ventricle physiology (intra-cardiac or extra-cardiac tunnel type of Fontan-completion, at least 2 stages, completed before the age of 6 years). Patients were treated at one of the 5 participating centres of paediatric cardiology in the Netherlands: Academic Medical Centre Amsterdam, Erasmus MC Rotterdam, Leiden University Medical Centre, University Medical Centre Radboud Nijmegen, and University Medical Centre Utrecht.

Excluded were patients who were > 17 years, and those with: contra-indications for exercise, mental retardation, standard contra-indications for MRI, or a ventricular outflow obstruction (peak Doppler gradient > 60 mm Hg).

Randomization

After informed consent had been obtained, patients received an anonymous study code and were invited for psychological and medical *baseline* assessments. Then a 'blind' independent researcher allocated them to the exercise group or the control group; ratio 2:1, restricted randomization: stratified by age, gender, and cardiac diagnosis.

Intervention

The standardized exercise program consisted of 3 training sessions of 1 hour per week, during a 12-week period. Children who already participated in other sports activities participated in 2 training sessions per week. Aerobic training consisted of dynamic exercise at 60-70% of heart rate reserve, measured by heart-rate monitors. The program was performed group-wise, under supervision of a trained physiotherapist in local physiotherapy-centres throughout the Netherlands. The control group continued their normal daily live and were invited for a baseline and a follow-up medical and psychological assessment.

Assessment procedure

The research protocol was approved a priori by the ethics-committee review boards of all 5 medical centres and complies with the 1975 Declaration of Helsinki. All eligible patients and

their parents were approached uniformly. All participating patients signed informed consent before participating. Then patients and parents completed the same psychological instruments at 2 points in time. At baseline, a web-based questionnaire and a semi-structured interview by phone were completed no longer than 2 months before the start of the exercise program, and 1-3 days before the baseline cardiac assessment in the hospital. The second assessment was performed no later than one month after completion of the exercise program, and no more than 2 weeks after the second cardiac assessment in the medical centre. Assessments for control groups were performed at comparable timepoints.

Instruments

Biographical data were assessed with a semi-structured interview[12]. Socioeconomic status was divided into low, middle, and high occupational level[13].

Emotional and behavioural problems

Child Behavior Checklist (CBCL)[14] was used to obtain standardized parents' reports of emotional and behavioural problems in their child. The problem section of the CBCL contained 120 items which can be comprised in 8 specific syndrome-scales, two broad problem areas: internalizing problems and externalizing problems, and one total problem score, see Table 2. Internalizing problems reflects internal distress and externalizing problems reflects conflicts with other people. A higher score indicates a higher level of problems. The original CBCL recall-period is 6 months; because of the intervention period, it was changed into 3 months. The CBCL norm-group consisted of 1417 parents of Dutch children, aged 6 to 16[15].

Youth Self Report (YSR)[14] the parallel version of the CBCL, was used to obtain standardized adolescents' self-reports of emotional and behavioural problems. The YSR norm-group consisted of 810 Dutch children, aged 11 to 18[15].

Anxiety for sports

The *Anxiety thermometer (AT)* was specifically developed for this study to assess anxiety for sports. Its format is derived from the 'feelings-thermometer' of the internationally standardized Anxiety Disorders Interview Schedule (ADIS-C)[16] showing 9 thermometers with increasing values (0 - 8). Since the AT was specially developed for this study; no normative data were available.

Statistical analyses

Statistical analyses were based on the intention-to-treat principle. Pre-post changes in exercise group versus control group were compared using MANOVAs, followed by separate univariate ANOVAs. Changes within the exercise group respectively control group were analysed with paired-sample-t-tests. Effect sizes (ES) for each pre-post change (Δ) were calculated.

Due to small groups, gender-specific pre-post changes were compared with Mann-Withney tests ($p<.05$). Repeated measurements within the exercise group and control group were analysed with Wilcoxon Signed Ranks Tests.

Comparisons with normative groups were calculated using Students't tests. Influences of gender, age, and cardiac diagnosis were estimated using generalized linear models. Statistics were conducted using SPSS version 20.0.

RESULTS

Biographical data

At the start of the study, 362 eligible patients, 61% male, 36% Fontan were contacted, of whom 26% finally participated (Figure 1). The final sample included 71 participants, median age: 14 years, 70 % male, 52% Fontan, 48% ToF; socioeconomic status (SES): high 47%, middle 39%, low 11%, missing 3%.

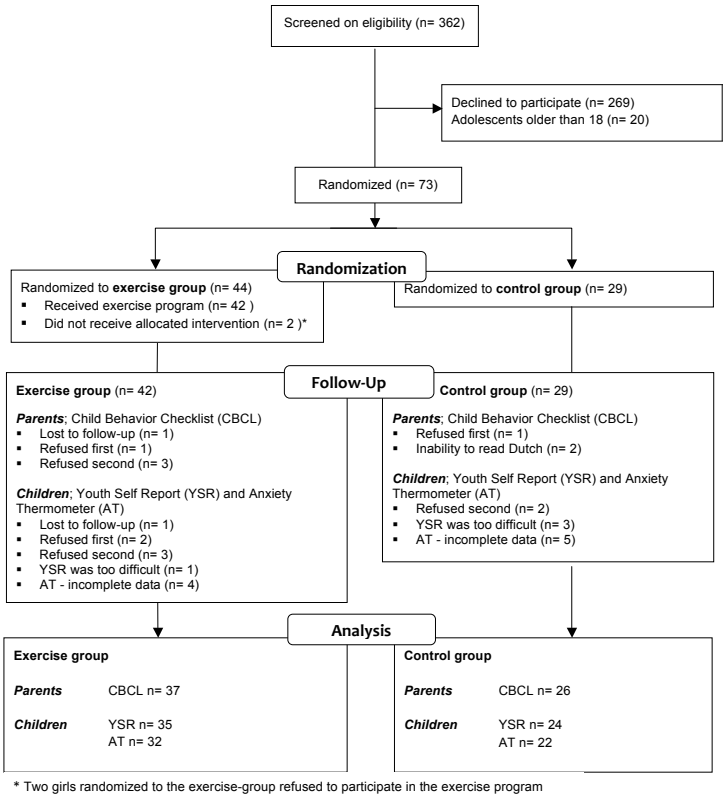

Figure 1: Enrollment in study

No differences between the exercise group and control group were found on demographical characteristics, on baseline cardio-respiratory fitness, on baseline participation in sports activities (Table 1) or on baseline emotional and behavioural problems (Table 2).

Table 1: baseline demographic characteristics

	Exercise group n=42	**Control group n=29**
Demographic status		
Age in years	14.0 (12.1 - 15.7)	14.9 (12.7 - 16.0)
Male	30 (71.4)	20 (69.0)
Congenital heart disease		
Tetralogy of Fallot	20 (48)	14 (48)
Age at ToF operation	0.5 (0.3 -0.8)	0.7 (0.5 – 1.0)
Fontan circulation	22 (52)	15 (52)
Age at Fontan completion	2.9 (2.5 – 4.0)	3.0 (2.4 – 4.3)
Social economic status		
Low (1)	5 (12)	3 (10)
Middle (2)	16 (38)	12 (42)
High (3)	20 (48)	13 (45)
Missing	1 (2)	1 (3)
Cardio- respiratory fitness		
*PeakVO_2 (% predicted)**	79.8 (16.0)	81.8 (18.7)
Peak load (Watt)	126.4 (44.5)	139.7 (46.5)
Peak heart rate (bpm)	169.5 (21.5)	176.5 (16.1)
VE/VCO_2 slope	29.0 (5.3)	30.2 (7.4)
Participation in sports activities		
Never	4 (10)	3 (10)
1-4 hpw	26 (62)	15 (52)
>5 hpw	12 (29)	11 (38)

Demographic status and participation in sports activities: data are presented as number (percentage), age is presented as median (inter quartile range).

Cardio-respiratory fitness: data are presented as mean (standard deviation).

* n = 9 missing values due to unsuccessful cardiopulmonary exercise test (respiratory exchange ratio (RER) < 1.0.)

Hpw = hours per week, bpm = beats per minute.

Table 2: Child Behaviour Checklist and Youth Self Report mean scores

	Child Behaviour Checklist						Youth Self-Report					
	Exercise group (n=37)		Control group (n=26)		p value		Exercise group (n=35)		Control group (n=24)		p value	
Scales	Baseline	Follow-up	Baseline	Follow-up	Δexercise versus Δcontrol	Effect-size	Baseline	Follow-up	Baseline	Follow-up	Δexercise versus Δcontrol	Effect-size
Anxious/Depressed	2.5 (2.4)	2.2 (2.4)	2.7 (3.4)	1.3 (2.5) [c]	0.06	.24	2.9 (3.0)	2.8 (2.7)	3.3 (3.9)	2.4 (3.4)	0.24	.16
Withdrawn/Depressed	2.6 (2.3)	2.3 (2.3)	2.0 (1.9)	1.5 (1.7)	0.57	.07	2.3 (1.9)	2.3 (2.5)	2.7 (2.1)	1.5 (1.8) [c]	0.05 [a]	.26
Somatic Complaints	2.5 (2.0)	2.4 (2.7)	3.2 (1.7)	2.0 (1.9) [c]	0.03 [a]	.28	3.0 (2.1)	2.3 (2.6) [b]	3.4 (2.6)	2.4 (2.2) [c]	0.61	.07
Social Problems	2.9 (2.2)	2.8 (2.8)	2.0 (2.9)	1.7 (2.9)	0.51	.08	3.9 (3.0)	2.7 (2.9) [b]	3.4 (3.0)	2.5 (2.8) [c]	0.79	.04
Thought Problems	2.2 (2.5)	1.9 (2.2)	2.0 (2.6)	1.7 (2.4)	0.92	.01	2.9 (2.5)	2.9 (2.8)	2.8 (2.3)	2.3 (2.4)	0.56	.08
Attention Problems	5.6 (3.1)	4.8 (2.9)	4.7 (4.1)	4.6 (3.7)	0.28	.14	5.1 (3.0)	5.0 (3.2)	5.3 (3.6)	4.7 (3.7)	0.54	.08
Rule-Breaking Behaviour	1.2 (1.3)	1.0 (1.5)	1.8 (1.8)	1.6 (1.5)	0.84	.03	2.7 (1.8)	2.7 (2.7)	3.2 (3.0)	2.5 (2.5)	0.26	.15
Aggressive behaviour	3.6 (3.6)	3.0 (3.7)	4.4 (3.6)	3.9 (4.0)	0.94	.00	3.7 (3.1)	3.2 (3.8)	5.0 (3.5)	3.8 (3.4)	0.38	.12
Internalizing	7.6 (5.0)	6.9 (6.3)	7.9 (5.6)	4.9 (4.7) c	0.04 [a]	.26	8.3 (5.7)	7.3 (6.4)	9.3 (7.6)	6.3 (5.2) [c]	0.09	.22
Externalizing	4.8 (4.6)	4.0 (5.1)	6.2 (4.7)	5.5 (5.2)	0.99	.00	6.4 (4.3)	5.9 (5.8)	8.2 (5.6)	6.3 (5.2)	0.27	.15
Total Problems	26.8 (14.0)	23.1 (16.8)	25.7 (16.4)	21.0 (17.0)	0.71	.05	30.3 (16.1)	26.9 (19.7)	32.7 (17.9)	25.0 (17.3) [c]	0.26	.15

Data are presented as mean (standard deviation), a) Significant pre-post change (Δ) in exercise group versus control group; $p<0.05$, b) Significant change from pre-to-post within exercise group; $p<0.05$, c) Significant change from pre-to-post within control group; $p<0.05$. Effect size (ES) for each pre-post change (Δ) was calculated.

Statistical analyses were on intention-to-treat principle: pre-post changes (Δ) in the exercise group vs. control group with multivariate analysis of variance repeated measures test, changes within each group with paired-sample-t-tests.

Effects of an exercise program on emotional and behavioural problems and anxiety

Child Behaviour Checklist

From pre- to post assessment, parents in the control group reported a decrease in somatic complaints ($p < .05$, $ES = .28$), internalizing problems ($p<.05$, $ES = .26$), and a trend towards less anxious/depressed problems ($p = .06$, $ES = .24$), regarding their children compared with parents in the exercise group (Table 2).

Within the exercise group, parents did not report any change from pre-to post assessment regarding their child. Parents in the control group reported less anxious/depressed problems ($p<.01$, $ES = .53$) and somatic complaints ($p<.01$, $ES = .56$) from pre-to post assessment.

Youth Self-Report

Comparing pre-post changes, adolescents in the control group reported a greater decrease of withdrawn/depressive problems ($p<.05$, $ES = .27$) than those in the exercise group (Table 2).

Considering pre-post changes within the exercise group, adolescents themselves reported a decrease of somatic problems ($p<.05$, $ES = .37$) and social problems ($p<.01$, $ES = .43$). Within the control group, however, adolescents did not only report fewer problems on these same scales from pre-to post assessment, but they also reported fewer withdrawn/depressed problems ($p<.05$, $ES = .46$), internalizing problems ($p<.01$, $ES = .46$), total problems ($p<.01$, $ES = .45$), and a trend towards anxious/depressed problems ($p = .06$, $ES = .39$).

Anxiety thermometer (AT)

No significant pre-post change was found on the AT between the exercise group and the control group. Considering pre-post change within each group, adolescents in the exercise group reported less anxiety ($M\Delta = -0.56$) for sports during follow-up $t(40)=-2.37$, $p<.05$, $ES = .35$, whereas control-children did not.

Comparison at follow-up with gender-specific normative data

Child Behaviour Checklist

At follow-up, parents in the exercise group reported more somatic complaints and social problems (both $p<.05$, $ES = .42$ and $.43$), but less rule-breaking behaviour and externalizing problems (both $p<.05$, $ES = .62$ and $.38$) regarding their sons than parents from the general population (see Table 3). For daughters, parents in the exercise group reported lower rule-breaking behaviour than parents in the general population ($p<.05$, $ES = .68$).

Table 3: Child Behavior Checklist and Youth Self-Report mean scores; comparison with gender reference groups

	Boys						**Girls**					
	Exercise group (n=27)		Control group (n=18)		p value Δexercise vs Δcontrol	Healthy reference	Exercise group (n=10)		Control group (n=8)		p value Δexercise vs Δcontrol	Healthy reference
CBCL syndrome scales	Baseline	Follow-up	Baseline	Follow-up			Baseline	Follow-up	Baseline	Follow-up		
Anxious/Depressed	2.6 (2.3)	2.1 (2.2)	2.6 (3.6)	1.7 (2.8)	0.47	2.5 (2.7)	2.4 (2.8)	2.4 (2.9)	3.0 (3.3)	0.6 (1.2) [b]	0.03 [a]	3.4 (3.1)
Withdrawn/Depressed	2.9 (2.4)	2.5 (2.3)	2.0 (1.8)	1.9 (2.0)	0.62	2.4 (2.3)	1.7 (1.9)	1.7 (2.5)	2.1 (2.4)	0.6 (0.5) [b]	0.13	2.5 (2.3)
Somatic Complaints	2.4 (1.8) [b]	2.1 (2.2) [b]	3.0 (1.8) b	1.9 (2.0)	0.15	1.1 (1.8)	2.7 (2.5)	3.3 (3.7)	3.5 (1.4) [b]	2.3 (1.6)	0.09	2.0 (2.3)
Social Problems	3.3 (2.2) [b]	3.1 (2.9) [b]	2.1 (3.0)	1.9 (3.3)	0.97	1.8 (2.1)	1.8 (2.1)	2.0 (2.4)	2.0 (2.9)	1.3 (1.6)	0.22	1.9 (2.2)
Thought Problems	2.4 (2.7)	2.1 (2.4)	1.9 (2.6)	1.9 (2.6)	0.58	1.6 (1.9)	1.7 (1.6)	1.3 (1.3)	2.0 (2.8)	1.1 (1.9)	0.50	1.8 (2.0)
Attention Problems	6.2 (3.0) [b]	5.0 (3.1)	4.9 (4.0)	5.3 (3.9)	0.02 [a]	4.1 (3.3)	4.0 (2.9)	4.3 (2.4)	4.1 (4.5)	3.0 (2.7)	0.31	3.3 (2.9)
Rule-Breaking Behaviour	1.2 (1.3) [b]	1.1 (1.5) [b]	1.6 (1.4) b	1.8 (1.6)	0.30	2.3 (2.7)	1.2 (1.3) [b]	0.9 (1.6) [b]	2.4 (2.6)	1.1 (1.4) [b]	0.19	2.3 (2.6)
Aggressive Behaviour	3.7 (3.9)	3.1 (3.9)	5.2 (3.9)	4.8 (4.3)	0.80	4.0 (4.2)	3.2 (2.7)	2.7 (3.3)	2.8 (2.3)	1.9 (2.3) [b]	0.73	4.2 (4.1)
Internalizing	7.9 (4.5) [b]	6.8 (5.6)	7.6 (5.6)	5.5 (5.4)	0.44	6.0 (5.3)	6.8 (6.6)	7.4 (8.2)	8.6 (5.8)	3.5 (2.4) [b]	0.04 [a]	7.9 (6.3)
Externalizing	4.9 (4.8)	4.2 (5.3) [b]	6.7 (4.8)	6.6 (5.5)	0.60	6.3 (6.2)	4.4 (3.9)	3.6 (4.8)	5.1 (4.6)	3.0 (3.6) [b]	0.41	6.5 (6.0)
Total Problems	28.3(13.1)[b]	23.9 (16.1)	26.0 (16.9)	24.2 (18.7)	0.39	22.6 (16.6)	22.6 (16.1)	21.2 (19.4)	25.1 (16.6)	14.0 (10.4) [b]	0.11	24.3 (17.0)

Table 3 *Continued*

	Boys						Girls					
	Exercise group (n=25)		Control group (n=16)		p value		Exercise group (n=10)		Control group (n=8)		p value	
YSR syndrome scales	Baseline	Follow-up	Baseline	Follow-up	Δexercise vs Δcontrol	Healthy reference	Baseline	Follow-up	Baseline	Follow-up	Δexercise vs Δcontrol	Healthy reference
Anxious/Depressed	2.9 (3.1)	2.5 (2.5)	2.1 (2.7)	2.1 (3.5)	0.71	3.1 (3.0)	3.1 (2.8) [b]	3.3 (3.2)	5.6 (5.2)	2.9 (3.5)	0.02 [a]	5.1 (3.8)
Withdrawn/Depressed	2.5 (1.8)	2.3 (2.6)	2.3 (1.8)	1.7 (2.2)	0.53	2.7 (2.1)	1.9 (2.1)	2.0 (2.5)	3.5 (2.5)	1.1 (0.8) [b]	0.01 [a]	3.1 (2.3)
Somatic Complaints	2.8 (2.0)	2.3 (2.7)	2.9 (2.6)	1.8 (2.1)	0.28	2.1 (2.2)	3.4 (2.5)	2.0 (2.4) [b]	4.4 (2.5)	3.6 (2.0)	0.45	3.8 (2.8)
Social Problems	3.8 (3.2)	3.1 (3.2)	3.1 (2.6)	2.2 (2.7)	0.79	2.9 (2.3)	4.1 (2.6)	2.1 (1.8) [b]	4.0 (3.8)	3.0 (3.0)	0.35	3.4 (2.4)
Thought Problems	3.0 (2.7)	3.1 (3.0)	2.4 (2.1)	2.3 (2.8)	0.67	2.9 (2.6)	2.8 (2.0)	2.0 (2.0)	3.5 (2.6)	2.4 (1.8)	0.76	3.4 (2.9)
Attention Problems	5.5 (3.4)	5.1 (3.5)	4.7 (3.5)	4.6 (3.3)	0.75	4.9 (3.0)	4.2 (1.5)	4.9 (2.5)	6.4 (3.7)	4.9 (4.8)	0.04 [a]	5.1 (3.0)
Rule-Breaking Behaviour	2.5 (1.8) [b]	2.5 (2.9) [b]	3.4 (2.4)	3.2 (2.6)	0.60	4.0 (3.2)	3.2 (1.6)	2.9 (2.3)	2.6 (4.0)	1.1 (1.6) [b]	0.29	3.8 (2.8)
Aggressive Behaviour	3.5 (3.0) [b]	3.0 (3.9) [b]	5.1 (3.3)	4.2 (3.5)	0.65	4.9 (3.9)	4.2 (3.5)	3.6 (3.3)	4.9 (4.0)	3.1 (3.3)	0.34	5.5 (3.8)
Internalizing	8.2 (5.4)	7.0 (6.1)	7.3 (6.1)	5.6 (6.8)	0.62	7.9 (5.9)	8.4 (6.7)	7.3 (7.4)	13.5 (8.8)	7.6 (4.1) [b]	0.05 [a]	12.0 (7.2)
Externalizing	6.0 (4.4) [b]	5.5 (6.2) [b]	8.5 (4.7)	7.4 (5.3)	0.60	8.9 (6.5)	7.4 (4.4)	6.5 (4.4)	7.5 (7.4)	4.3 (4.8) [b]	0.23	9.3 (5.9)
Total Problems	30.2 (16.7)	26.8 (20.1)	29.4 (14.7)	24.9 (17.5)	0.75	31.3 (17.1)	30.7 (15.2)	26.0 (17.9)	39.4 (22.8)	25.3 (17.9)	0.10	37.6 (18.0)

Data are presented as mean (SD), a) Significant pre-post change (Δ) in exercise-group versus control-group; $p<0.05$, b) Significant change from healthy reference; $p<0.05$

Parents in the control group reported at follow-up similar levels of problems compared with normative data, regarding their sons. As to daughters, parents in the control group reported less anxious/depressed problems, withdrawn/depressed problems, rule-breaking behaviour, aggressive behaviour, internalizing problems, externalizing problems, and total problems than parents in the general population (all $p<.05$, *ES* varying between .68 and .96).

Youth Self Report

In the exercise group, boys obtained lower scores at follow-up as to rule-breaking behaviour, aggressive behaviour, and externalizing problems compared with boys from the general population, all $p<.05$, *ES* varying between .42 and .46 (see Table 3). Girls reported less somatic complaints and social problems compared with so-called normative girls, both $p<.05$, $ES = .62$ and .61.

Regarding the control group, girls reported less withdrawn/depressed problems, rule-breaking behaviour, internalizing and externalizing problems compared with normative data, all $p<.05$, *ES* varying between .75 and .93. Boys reported comparable scores as normative data.

Influence of gender, age, and cardiac diagnosis

Gender

Girls in the exercise group did not change as to internalizing problems, whereas girls in the control group improved on internalizing problems from baseline to follow-up. Boys in both the exercise group and control group had comparable pre-post improvements (see Figure 2). Parents showed a similar interaction effect between gender and study-group as to internalizing problems (see Figure 2).

Age

The older girls in the control group, the more improvements as to internalizing problems they reported. In the exercise group, however, age had no influence on changes in internalizing problems in girls; in boys no influence of age was found in both study-groups.

Cardiac diagnosis

had no influence on changes in emotional and behavioural problems from baseline to follow-up.

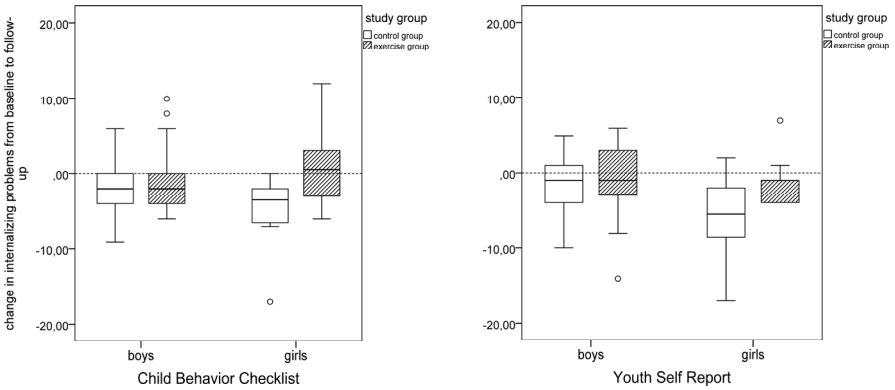

Figure 2: Change from baseline to follow-up in internalizing problems in exercise group and control group, split for gender

DISCUSSION

The most important outcome of this RCT was that a 12-week standardized exercise program, overall, had no positive effect from pre-to post assessment on emotional and behavioural problems in adolescents with ToF or Fontan circulation. These are diagnostic categories with the poorest long-term cardiac outcome[17].

Our findings are in contrast with the more positive outcomes of the few smaller, non-randomized studies in the field[8-10]. The only intervention-study that also assessed emotional and behavioural problems[8] used two exercise programs; either a 2-week exercise program in a rehabilitation centre, or a 5-month exercise program near their homes. A small number of adolescents with varying ConHD diagnoses were enrolled and they were compared with voluntary peers with ConHD. Participation in any of the two exercise programs resulted in lower parent-reported internalizing problems, withdrawn/depressed problems, and somatic complaints. As to self-reports, no differences on any emotional and behavioural scale were found.

The two other studies[9, 10] investigated the influence of an exercise program in adolescents with ConHD on health status, both using the Child Health Questionnaire (CHQ- Parent and Child Form)[18]. Moons et al.[9] reported that children with several diagnoses of ConHD, who attended a 3-day sports camp, improved on self-esteem and general behaviour. Rhodes et al.[10] compared 15 youngsters with complex ConHD who followed a 12-week exercise program with voluntary controls who had similar diagnoses. One year later, the exercise group reported clinically important improvements in their emotional, behavioural, and physical state.

These studies, however, shared methodological flaws, e.g. small samples, non-standardized exercise programs, many dropouts. In our multi-centre study, we used relatively larger samples, a standardized exercise program, and a randomized control group. Moreover, our drop-out rate was very low, only 2 girls randomized to the exercise group refused to participate in the exercise program, and one girl did not complete the total intervention.

Surprisingly, our study showed that adolescents in the control group reported significant greater pre-post improvements on withdrawn/depressed problems compared with adolescents in the exercise group. Parents in the control group reported significantly greater improvements in somatic complaints and internalizing problems compared with parents in the exercise group. As to anxiety for sports, no significant pre-post changes between the exercise group and control group were found.

As to changes within the study groups, adolescents in the exercise group reported a decrease in anxiety for sports at follow-up, whereas those within the control group did not. And adolescents and their parents in the control group "only", reported improvements on internalizing problems (on most subscales: anxious/depressed, withdrawn/depressed, somatic complaints).

We should be careful drawing firm conclusions about gender effects, considering the smaller subsamples for gender. However, we want to underline the following remarkable results. Overall, pre-post improvements were found in the control group on internalizing subscales. Since boys in the exercise- versus control group did not change on internalizing problems, these improvements can be mainly attributed to girls, especially the *older* girls. These interaction effects became apparent on both self-reports and parent-reports. Improvements in internalizing problems are important, since Karsdorp et al.[3] found in a meta-analysis that parents of children and adolescents with ConHD reported more internalizing and total problems in their children compared with normative data.

A possible explanation might be that (older) girls, who are already very busy with school and other activities, may feel relieved from a possible burden to participate in an exercise program three times a week. It is known that in the general population, girls get less physically active when they enter adolescence, whereas boys do not[19]. In a qualitative study of Moola et al.[20] adolescents with ConHD reported that they were not interested and motivated for physical activities. The majority indicated that sport was not a valuable pursuit. However, these outcomes were not gender specific.

Besides possibly feeling relieved about non-participation in exercise, an advantage of taking part in this study might be that girls in the control group obtained a feeling of safety and assurance receiving two psychosocial and physical assessments. Girls are more inclined than boys to disclose problems and share emotions[21]. They may have benefited from this possibility to express emotions in interviews with the psychologist and through questionnaires. Adolescents in the exercise group obtained the same psychosocial and physical assess-

ments. Although adolescents in the exercise group had less anxiety for sports at follow-up, they did not change on generic internalizing problems (YSR). Participation in an exercise program may have been a burden in effort and time. It may have also confronted them with their physical limitations, making them aware of being a person with limitations due to their heart disease. From literature[22, 23], it seems that psychosocial needs in these adolescents are a neglected but important field.

From qualitative studies it is known that parents of ConHD adolescents might be overprotective and anxious towards participation in sports[24, 25]. This might also be the reason for our low response rate (26%) in this study. Parents in the control group reported less somatic complaints and internalizing problems at follow-up. The extra check-ups may have given them a feeling of safety and care. They also may feel relieved that their child did not have to test its limits in a sports program. Besides anxiety, a real logistic burden may have played a role.

Comparison with normative data at follow-up

As to ConHD children, several researchers reported elevated levels in internalizing problems, but also in externalizing problems[26, 27], aggressive behaviour[27, 28], attention problems[27-29], and total problems[3]. In contrast, parents in both groups reported comparable or lower scores for these problem scales at follow-up compared with normative data. This may be the result of selection-bias for this randomized controlled trial.

As to internalizing problems, only parents of girls in the control group reported better scores at follow-up compared to normative data. In line with our previous conclusions that parents within the control group reported pre-post improvements in internalizing problems, they also obtained better scores compared to normative data.

Study strengths and limitations

As to strengths, this is a multi-centre, randomized controlled trial with a standardized exercise program and assessment instruments. Considering previous research, our sample was larger and the dropout rate was very low. As to limitations, the response-rate of this study was low, especially that for girls, and therefore at times, sub-analyses had lack of power.

Conclusions

A standardized exercise program in adolescents with ConHD did not influence emotional and behavioural problems. Surprisingly, control-girls and their parents reported improvements as to internalizing problems after a period with two medical and psychological examinations, and contact with a psychologist. These contact moments, together with the knowledge that they did not have to exercise three times a week, might have relieved them and made them feel less anxious and depressed. On the other hand, adolescents who did

participate in an exercise program reported less anxiety for sports, whereas control-adolescents did not.

Since our randomized controlled trial, overall, showed few effects of an exercise program, this clearly indicates a need for future research. First, another follow-up moment could unravel longer-term sleeper effects. Beside this, possibly the content, intensity, and duration of the intervention was not sufficiently attuned to the needs and preferences of the patients. Future research should focus on how an exercise program can be tailored to individual needs.

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Chapter 5

Effects of an exercise program on sports enjoyment and leisure time spending in adolescents with complex congenital heart disease; the moderating influence of health behaviour and disease knowledge

Karolijn Dulfer, Nienke Duppen, Nico A. Blom, Arie P.J. van Dijk, Willem A. Helbing, Frank C. Verhulst, Elisabeth M.W.J. Utens

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ABSTRACT

Aim

To evaluate effects of a standardized exercise program on sports enjoyment and leisure time spending in adolescents with congenital heart disease; what is the moderating impact of their baseline health behaviour and disease knowledge.

Methods

Included were 93 patients, aged 10 to 25, with surgical repair for tetralogy of Fallot (ToF) or with a Fontan circulation for single-ventricle physiology, of 5 participating centres of paediatric cardiology in the Netherlands. They were randomly allocated, stratified for age, gender, and type of ConHD to: a) a 12-week period with an exercise program for 3 times per week or b) to a control group (randomization ratio 2:1). At baseline and after 12 weeks, participants completed web-based questionnaires and were interviewed by phone.

Main outcome measures

Primary analyses tested pre-post changes in sports enjoyment and leisure time spending in the exercise group versus control group. Secondary analyses concerned the moderating influence of baseline health behaviour and disease knowledge on pre-post changes, and comparison with normative data.

Results

At follow-up, the exercise group reported a decrease in passive leisure time spending (watching television and computer usage) compared with controls. An exercise program had no effect on sports enjoyment and active leisure time spending. Disease knowledge had a moderating influence on improvement in sports enjoyment, whereas health behaviour did not. Compared with normative data, patients obtained similar leisure time scores and lower frequencies as to drinking alcohol and smoking.

Conclusions

An exercise program decreased passive, but not active leisure time spending. It did not influence sports enjoyment.

INTRODUCTION

Contemporary outcomes for paediatric cardiac surgery are good; nowadays about 85% of children born with moderate or serious congenital heart disease (ConHD) survive into adulthood[1]. In adulthood, risk for complications and early mortality in adults with ConHD is larger than in adults from the general population. Complications and early mortality are mainly caused by cardiac related issues; e.g. cardiac surgery, heart failure, sudden death and other cardiovascular diseases[2]. To prevent or delay these complications, it is important for patients with ConHD to pursuit an optimal healthy lifestyle, including participation in daily activity and sports, together with avoidance of risky health behaviour. Healthy lifestyle and risk factors commonly are developed in adolescence and persist into adulthood[3].

In adolescents from the general population, well-known lifestyle risk factors are: physical inactivity, unhealthy diet behaviour, and substance abuse[3-7]. Adolescents with ConHD also present these lifestyle risk factors: they tend to become more obese or overweight[8] they do not achieve 60 min of recommended daily moderate-to-vigorous physical activity[9] and have unhealthy diet behaviours[10]. They also use alcohol, cigarettes, and drugs on regularly basis[11]. Besides this, they are also at risk for condition-related cardiovascular disease[10] and are therefore they are advised to pursuit good oral hygiene to avoid infective endocarditis[11], to use contraception responsibly, and to avoid risky sexual behaviour[12].

Pemberton et al.[2010] formulated guidelines[13] aimed to improve health behaviour in children with ConHD. These guidelines addresses diet behaviour (reducing excessive energy intake) and leisure time spending (limiting screen time, i.e. television and computer usage). They are also aimed at increasing energy expenditure to more than 60 minutes of moderate to vigorous physical activity daily.

A useful tool to increase energy expenditure in adolescents with ConHD is an exercise program. Such a program may improves physical fitness; i.e. PeakVO2, activity levels, and muscle strength[14]. Sports enjoyment is one of the main reasons reported by adolescents in the general population to participate in sport and physical activity[15], therefore this is also an important target for ConHD-adolescents.

Since unhealthy risk factors are formed in adolescence, it is important that adolescents with ConHD have proper disease knowledge about growing up with their disease and that they have insight in their health behaviour and possible risk factors[16].

It has not yet been investigated, to the best of our knowledge, whether an exercise program influences sports enjoyment and self-reported leisure-time spending in adolescents with ConHD. In addition, the influence of baseline health behaviour and disease knowledge is also unknown.

This study is the first, aiming to answer the following questions:

1. What is the effect of a 12-week standardized exercise program in children, adolescents, and young adults (10-25 years of age) who have undergone treatment for tetralogy of Fallot (ToF) or have a Fontan circulation on their sports enjoyment and leisure time spending?
2. What is the moderating impact of baseline health behaviour and disease knowledge?
3. What are levels of sports enjoyment and leisure time spending compared with normative data. And what are those of baseline disease knowledge and health behaviour?

METHODS

This randomized controlled trial is designed according to the CONSORT guidelines[17].

Inclusion/exclusion

Included were patients aged 10 to 25, who underwent cardiac surgery before the age of 2 for ToF or who underwent surgery for single-ventricle physiology (intra-cardiac or extra-cardiac tunnel type of Fontan-completion, at least 2 stages) completed before the age of 6 years. Patients were treated at one of the 5 participating centres of paediatric cardiology in the Netherlands: Academic Medical Centre Amsterdam, Erasmus MC Rotterdam, Leiden University Medical Centre, Radboud University Nijmegen Medical Centre, and University Medical Centre Utrecht.

Excluded were patients with contra-indications for exercise, mental retardation, standard contra-indications for MRI, or a ventricular outflow obstruction (peak Doppler gradient > 60 mm Hg).

Randomization

After informed consent had been obtained, patients received an anonymous study code and were invited for psychological and medical *baseline* assessments. Then a 'blind' independent researcher allocated them to the exercise group or the control group; ratio 2:1, restricted randomization: stratified by age, gender, and cardiac diagnosis.

Intervention

The standardized exercise program consisted of 3 training sessions of 1 hour per week, during a 12-week period. Patients who already participated in other sports activities were instructed to continue these activities and participate in the exercise program 2 times a week. The exercise program consisted of 10 minutes warming-up, 40 minutes aerobic dynamic cardiovascular training, and 10 minutes cooling down. Participants were given a heart rate monitor to perform their exercises within the given heart range (resting heart rate plus 60-70

% of the heart rate reserve). This range was determined by the ergometer-test performed at the baseline assessment. The program was performed group-wise with other children/adolescents with a chronic illness, under supervision of a trained and licensed physiotherapist in local centres throughout the Netherlands. The same researcher (ND) visited all participating physiotherapists prior to the start of the program and visited them thereafter when needed, to ensure standardized implementation of the exercise program. The control group continued their normal daily live and were invited for a baseline and a follow-up medical and psychological assessment.

Assessment procedure

The ethics-committee review boards of all 5 participating medical centres approved the research protocol. All eligible patients and their parents were approached uniformly. After having signed informed consent, patients and parents completed the same psychological instruments at 2 points in time. At baseline, a web-based questionnaire and a semi-structured interview by phone were completed, no longer than 2 months before the start of the exercise program, and 1-3 days before the baseline cardiac assessment in the hospital. The second assessment was performed no later than one month after completion of the exercise program, and no more than 2 weeks after the second cardiac assessment in the medical centre. Assessments for control groups were performed at comparable timepoints.

Instruments

Biographical data were assessed with a semi-structured interview[18]. Socioeconomic status was divided into low, middle, and high occupational level[19].

Sports enjoyment

The 10-item Groningen Enjoyment Questionnaire (GEQ) was used to assess enjoyment in leisure-time physical activity[20]. The GEQ was originally developed for sedentary older adults. For our study, the GEQ has been adapted for children and adolescents. The GEQ has satisfactory reliability and validity[20].

Leisure time spending

The Rotterdam Leisure-time Spending Questionnaire (RLSQ)[21] was developed to assess leisure time spending (LTS), It was based on data obtained from the Dutch Central Bureau for Statistics[22]. Both active LTS (participation in sports, walking and cycling,) and passive LTS (computer and television usage) were assessed in a semi-structured interview by phone.

Health Behaviour

The Rotterdam Health Behaviour Questionnaire (RHBQ)[23] was developed to assess health behaviour. It was based on the Annual Report 2012 National Youth Monitor[22] and Youth Risk

Behaviour Surveillance System (YRBSS)[24]. Dichotomized items into alcohol usage (never/monthly or less versus 2 - 4 times per month or more) and smoking (no versus yes) were included.

Disease knowledge

The Rotterdam Knowledge Questionnaire (TRKQ)[25] assessed knowledge about ConHD. This questionnaire was based on Leuven Knowledge Questionnaire for Congenital Heart Disease[26]. Dichotomized items used were "What is the name of your congenital heart disease?" and "What is endocarditis?".

Statistical Analyses

Pearson's χ^2-tests tested differences between the exercise group and control group as to distributions of gender, cardiac diagnoses, and socioeconomic status. These tests were also used to compare leisure time spending and health behaviour frequencies with normative frequencies. If cell values were lower than 5, Fishers exact tests were used.

Nine participants in the exercise group and 8 participants in the control group did not fill in the first and/or the second sports enjoyment questionnaire; therefore multiple imputation was used to estimate these missing data[27]. Pre-post difference in sports enjoyment between the exercise group and control group was estimated with univeriate regression. The pooled coefficient that takes into account variation across imputations is reported.

Pre-post differences in ordinal variables between groups were compared with Mann-Whitney U tests.

To analyse the impact of moderators, these variables were added as factors (categorical data) or covariates (continuous variables) in the MANOVA repeated measures test. Statistics were conducted using SPSS version 20.0.

RESULTS

Biographical data

Eligible patients (n=362) were contacted of whom 93 (26%) finally participated (see Figure 1). Two girls refused to participate in the exercise group after the first assessment. The remaining sample consisted of 91 patients; median age 15.4 (IQR 12.8 - 17.7), 64/91 male, 47/91 ToF, 44/91 Fontan, socioeconomic status: low 12%, moderate 39%, high 49%. Patients were recruited and followed-up between January 2010 and August 2012.

At baseline, no differences were found between the exercise group versus control group on distributions of age, gender, cardiac diagnosis, socioeconomic status, sports enjoyment, passive leisure time spending, active leisure time spending, health behaviour, and disease knowledge, see Table 1 and Table 2..

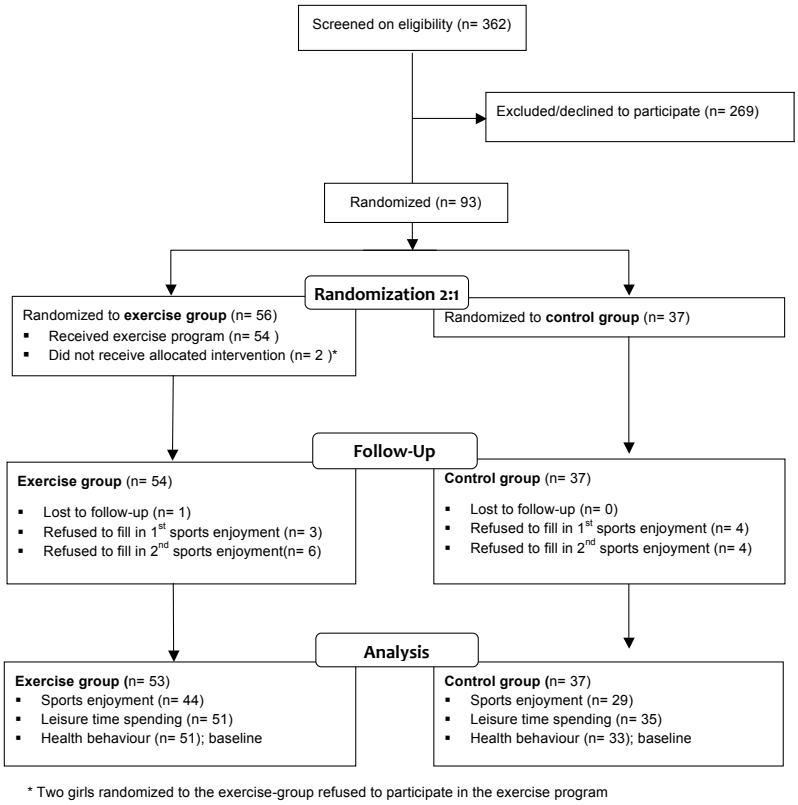

Figure 1: Enrollment in study

Table 1: Baseline demographic characteristics

	Exercise group n=54	Control group n=37
Age in years	15.2 (12.6-17.6)	15.5 (13.3-17.8)
Male	39 (72)	26 (70)
Congenital heart disease		
Tetralogy of Fallot (ToF)	27 (50)	20 (54)
Age at ToF operation	0.5 (0.4 – 1.1)	0.7 (0.5 – 0.9)
Fontan circulation	27 (50)	17 (46)
Age at Fontan completion	3.0 (2.5 - 5.0)	3.0 (2.5 – 3.9)
Social economic status		
Low (1)	6 (11)	4 (11)
Middle (2)	18 (33)	16 (43)
High (3)	29 (54)	14 (38)
Missing	1 (2)	3 (8)

Data are presented as number (percentage), only age is presented as median (IQR)

Effects of an exercise program on sports enjoyment and leisure time spending

Adolescents in the exercise group versus the control group did not change their sports enjoyment from pre- to post-assessment, b = -.79, *s.e.* = .82, t=-.96, p =.34 (Table 2).

Adolescents in the exercise group reduced their passive leisure time spending (LTS) compared with those in the control group, who increased their passive LTS, U = 528.00, z = -3.14, p <.01, r = -.34. As to active LTS, adolescents in both groups reported no change, U = 916.00, z = -0.02, p = .99, r =.00.

Age, gender, and cardiac diagnosis did not influence these differences.

Moderating impact of baseline health behaviour and disease knowledge

Changes in sports enjoyment were not influenced by smoking, $F(1,67) = 0.22$, p=.64, drinking alcohol, $F(1,67) = 1.61$, p=.29, nor by knowledge about the name of their ConHD, $F(1,57) = 1.03$, p=.36.

Improvements in *sports enjoyment* between the exercise group and the control group were influenced by knowledge about endocarditis, $F(1,57) = 5.44$, p<.05. Adolescents in the exercise group who knew about endocarditis reported more improvement.

Changes in *active LTS and passive LTS* were not influenced by smoking, $F(2,71) = 1.62$, p =.21, drinking alcohol, $F(2,71) = 0.89$, p =.42, knowledge about endocarditis, $F(2,60) = 0.79$, p=.46, nor knowledge about ConHD-name, $F(2,60)$=2.95, p=.06. Univariate tests showed that knowledge about ConHD-name had a nearly significantly moderating influence on changes in active LTS between the exercise group and the control group, $F(1,61)$=3.73, p=.058.

Baseline and follow-up leisure time spending compared with normative data

Active LTS

Adolescents in the exercise group participated less hours per week in sports activities at baseline χ^2 (2) = 9.82, p <.01 and follow-up χ^2 (2) = 15.85, p <.01 than adolescents from the general population. Adolescents in the control group did not.

At follow-up, adolescents in the control group participated more in walking compared with normative data, χ^2 (2) = 7.79, p <.05, whereas those in the exercise group did not. At baseline, scores of both groups were comparable to normative data.

Both groups bicycled as much as adolescents from the general population at baseline as well as at follow-up.

Passive LTS

Adolescents from both groups reported less time watching television at follow-up, compared with normative data, all p<.05. At baseline, adolescents in the control group watched

Table 2: Sports enjoyment, leisure time spending, health behaviour, and disease knowledge scores

Outcome measures				Exercise group (n=51)		Control group (n=35)		Normative data (%)
				Baseline	Follow-up	Baseline	Follow-up	
Sports enjoyment				25.4	25.4	24.5	25.4	n.a.
Leisure time spending	**Active**	Sports	*Never*	9 (18)	7 (14)	7 (20)	3 (9)	11
			1-4 hpw	30 (59)	35 (69)	16 (46)	19 (54)	44
			>5 hpw	12 (23)	9 (18)	12 (34)	13 (37)	45
		Walking	*Never*	13 (25)	5 (10)	6 (17)	5 (14)	23
			1-4 hpw	32 (63)	37 (73)	21 (60)	19 (54)	62
			>5 hpw	6 (12)	9 (18)	8 (23)	11 (32)	15
		Cycling	*Never*	7 (14)	7 (14)	10 (29)	9 (26)	15
			1-4 hpw	28 (55)	29 (57)	18 (51)	19 (54)	59
			>5 hpw	16 (31)	15 (29)	7 (20)	7 (20)	26
	Passive	Television	*0-5 hpw*	11 (22)	8 (16)	9 (26)	3 (9)	15
			5-10 hpw	17 (33)	21 (41)	12 (34)	17 (49)	24
			10-20 hpw	17 (33)	17 (33)	11 (31)	10 (29)	41
			>20 hpw	6 (12)	5 (10)	3 (9)	5 (14)	22
		Computer	*0-1 hpd*	16 (31)	24 (37)	14 (40)	9 (26)	n.a.
			1-2 hpd	18 (35)	12 (24)	8 (23)	7 (20)	n.a.
			2-3 hpd	10 (20)	7 (14)	8 (23)	7 (20)	n.a.
			>3 hpd	7 (14)	7 (14)	5 (14)	12 (34)	n.a.

Predictors		Exercise group (n=51)	Control group (n=33)	Normative data (%)
		Baseline	Baseline	
Health behaviour	Smoking	1 (2)	2 (6)	20
	Alcohol usage	12 (24)	8 (24)	70
Disease knowledge about	Type of ConHD	38 (83)	29 (85)	n.a.
	Endocarditus	3 (7)	3 (9)	n.a.

Data are presented as number (percentage), only for sports enjoyment data are imputed; therefore the pooled mean is presented.

hpw=hours per week, hpd=hours per day, n.a. = not available

television less often, compared with normative data. For spending time on the computer, no normative data were available.

Baseline health behaviour compared with normative data

Since few adolescents in our sample smoked (3 out of 84; 4%), it was not possible to compare them statistically with normative data (20%), see Table 2. As to alcohol usage, 20 out of 84 (24%) adolescents in our sample used alcohol 2 - 4 times per month or more. This is less than adolescents from the normative data (70%), $\chi^2(1)= 86.6$, $p<.001$.

DISCUSSION

A 12-week standardized exercise program reduced self-reported passive LTS in adolescents with ConHD. It had no influence on sports enjoyment or on active LTS. More knowledge about endocarditis was associated with more pre-post improvements in sports-enjoyment in the exercise group. Unhealthy behaviour (smoking and drinking) had no moderating influence, nor on sports enjoyment, nor on LTS. Compared with normative data, adolescents in our sample walked and bicycled the same amount of time, however they participated less time in sports activities. They smoked and used alcohol less frequently than adolescents and young adults from the general population.

Only two studies in adolescents and adults with ConHD measured change in physical activity (PA) level after an exercise program; they both showed increase in objectively measured PA[28, 29]. We did not find comparable improvements in self-reported PA. Noteworthy, our adolescents reported a decrease in passive LTS (watching television and computer usage) after participation in a standardized exercise program. An explanation could be that adolescents were participating in the exercise program instead of watching television or using their computer at home. On the other hand, our finding is in line with findings of an RCT of Salmon et al.[30]. They found that adolescents from the general population reported reduced TV viewing after having undergone behavioural modification and/or motor skills interventions. However, they did not find an increase in physical activity. The lack of association between reducing TV viewing time and increasing time in daily PA in adolescents is also reported in a meta-analysis[31].

Sports enjoyment is a significant correlate of children's and adolescent's physical activity in the general population[15, 32]. We did not find changes in sports enjoyment after an exercise program. An explanation could be that adolescents with ConHD see sports as an instrumental purpose, as being important because of its health benefit[33] rather than fun. Presumably, although the exercise program was performed group wise most of the time, the context

of the exercise program may not be tailored enough to the needs of these adolescents, such as having fun and having a relaxed time together[34]. In adolescents from the general population, 'best-friends' dyads show similarities in physical activity participation[35]. Possibly, involving a friend who likes to sport in the exercise program may enhance sports enjoyment of adolescents with ConHD.

On the other hand, the lack of improvement in sports enjoyment may also be related to negative enforcement. Adolescents with ConHD may experience physical limitations in sports participation. Therefore they may have a lower sport performance than healthy adolescents, which may result in less sports enjoyment.

As to moderators, only knowledge about endocarditis influenced improvements on sports enjoyment. Surprisingly, only 8% of the adolescents with ConHD in our sample knew about endocarditis. This is even lower than the low percentage (21%) reported in Van Deyk et al.[16]. Because of this low percentage, it is difficult to generalize this moderating influence.

Several studies[16, 36, 37] showed poor disease knowledge in youngsters with ConHD; e.g. only 45% could name or describe their ConHD[16]. In contrast, 84% of our adolescents could name or describe their ConHD. This is not that surprising, since their type of ConHD was an inclusion criterion in our RCT, and was therefore described in the patient information letter. Knowledge about their ConHD had a nearly significant moderating influence on improvements in active LTS in the exercise group. Future research, using a larger sample, should replicate this.

Health behaviour; smoking cigarettes and drinking alcohol, did not moderate changes in sports enjoyment nor in LTS. This could be explained by the low prevalence of smoking and drinking alcohol in our sample. A small percentage (4%) of adolescents with ConHD smoked, which is in contrast with a longitudinal study reporting that 12% of Belgian and German adolescents with ConHD were active smokers[10]. However, their percentage was also lower than the norm in their healthy peers (20%).

As to drinking, 24% of our sample used alcohol 2 to 4 times per month or more. In the general population, 70% of adolescents use alcohol on regular basis. Adolescents in the general population that smoked and/or drank alcohol participated less in endurance sports[38]. Since, in our RCT, adolescents participated voluntary into an exercise program, they were motivated to participate in sports. This may reflect a motivation towards a healthy lifestyle and may partially explain the low prevalence of drinking and using alcohol.

Limitations

Though our RCT-sample is large for this field in research, for statistical analysis it is relatively small. Moreover, selection bias, such as sampling bias, may have occurred. 26% of the adolescents, of whom 70% male, with ToF or a Fontan circulation participated in our RCT. Patients gave their consent to participate, before they knew whether randomization would

allocate them to the exercise or control group. Thus our sample was motivated to participate in sports. This motivated sample may also explain the low frequencies of smoking and drinking alcohol. On the other hand, at baseline, no differences were found between the exercise group and the control group on a broad range of variables. To what extent selection bias has influenced our results regarding the effects of the exercise program, is unknown.

Clinical implications

Sports enjoyment is an important link between participation and adherence in physical activity[34]. An exercise program with only aerobic exercises under supervision of a physiotherapist is probably not valued as a fun leisure activity by adolescents with ConHD. Therefore, tailoring the program more to age-relevant needs of adolescents with ConHD may improve their sport enjoyment. For example, participation with a friend who likes to sport, in a more socially oriented exercise program, for example dancing, may improve their sports enjoyment, thereby improving their participation in physical activity during leisure time.

Although a large part of adolescents and young adults in our sample could name or describe their ConHD, only 8% could describe what endocarditis is. The gap in disease knowledge remains an important point of attention.

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Chapter 6

Parental mental health moderates the efficacy of an exercise program on health related quality of life in adolescents with congenital heart disease

Karolijn Dulfer, Nienke Duppen, Arie P.J. van Dijk, Irene M. Kuipers, Ron T. van Domburg, Frank C. Verhulst, Jan van der Ende, Willem A. Helbing, Elisabeth M.W.J. Utens

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ABSTRACT

Background

To evaluate the moderating influence of parental variables on changes in health related quality of life (HRQoL) in adolescents with Tetralogy of Fallot (ToF) or a Fontan circulation after participation in a standardized exercise program.

Design

A multicentre randomized controlled trial in which 56 patients, aged 10 to 15, were randomly allocated (stratified by age, gender and congenital heart disease) to: a) a 12-week period with an exercise program for 3 times per week or b) to a control group (randomization ratio 2:1). Adolescents and their parents filled in online questionnaires at baseline and at 12-week follow-up.

Methods

In this randomized controlled trial, primary analyses involved influence of parental mental health and parental social support for exercise on changes in the TNO/AZL Child Quality of Life Questionnaire Child Form at follow-up. Secondary analyses concerned comparing levels of parental characteristics with normative data.

Results

Compared with controls, adolescents in the exercise group reported a decrease in social functioning when their parents had more anxiety/insomnia or severe depression themselves. Adolescents also reported a decrease in social functioning when their parents showed poorer overall mental health themselves. Parents reported comparable or even better mental health compared with normative data.

Conclusions

The effect of a standardized exercise program on HRQoL changes in adolescents with ToF or a Fontan circulation is moderated by parental mental health, more specifically by parental anxiety/insomnia and severe depression.

INTRODUCTION

Due to advances in medical care over the past 30 years, survival rates of children with congenital heart disease (ConHD) have increased enormously. Nowadays, 85% of these children survive into adulthood[1]. After surgical treatment, children with ConHD may experience limitations such as a reduced exercise capacity[2], lower physical activity levels[3], and also impaired health related quality of life (HRQoL)[4, 5].

An exercise program may improve exercise capacity of children with ConHD[6]. However, despite well-known beneficial effects of physical activity, children with ConHD are less vigorously active than their healthy peers[3, 7]. Parental anxiety and overprotection may hamper participation of children with ConHD in physical activities[8, 9]. In adolescents from the general population, parental support for exercise is positively related to moderate-to-vigorous physical activity[10, 11].

Parental overprotectiveness towards participation in physical activity regarding their ConHD child may be the result of parental psychological factors such as: feelings of loss of control, uncertain long-term prognosis, and negative past experiences[9]. Besides, parental mental health and parental worries also appeared to be strong predictors for children's emotional adjustment, whereas disease severity and surgical factors were not[12, 13]. Berant et al.[14] found that a maternal avoidant attachment style in the period of ConHD diagnosis was associated with emotional problems and poor self-image in the children 7 years later.

Summarizing, previous studies showed that if parents are not anxious (regarding sports) and if they support their child regarding sports, this would have a beneficial influence on their child's sports participation.

To our knowledge, the role of parental variables on psychological effects of an exercise program in children with ConHD has never been studied before. These parental variables are moderators since they identify on whom and under what circumstances the intervention has different effects[15]. Our hypothesis is that parental variables such as parental mental health and parental social support for exercise may have a moderating influence on a standardized 12-week exercise program on HRQoL of children with ConHD.

The present study is a multi-centre, prospective, randomized controlled, intervention study into the effect of standardized exercise training in a cohort of children and adolescents, aged 10-15 years, with either tetralogy of Fallot (ToF) or a Fontan circulation. Two-third of both ToF respectively Fontan children were randomized to an aerobic exercise program; the remaining one-third served as controls.

This study's aims concern:

1. What is the moderating role of parental mental health and parental social support towards exercise on the effect of a 12-week exercise program in adolescents, aged 10-15,

with ToF or a Fontan circulation on HRQoL scores, compared with controls from pre-to post assessment?
2. What is the level of parental mental health and social support in the exercise group and in the control group at follow-up, compared with normative data?

METHODS

Participants

Between January 2010 and August 2012, 93 patients aged 10 to 25 who underwent surgery for either Tetralogy of Fallot or single-ventricle physiology (treated with the Fontan operation) were included. Patients were treated at one of the 5 participating centres of paediatric cardiology in the Netherlands: Academic Medical Centre Amsterdam, Erasmus Medical Centre Rotterdam, Leiden University Medical Centre, University Medical Centre Radboud Nijmegen, and University Medical Centre Utrecht.

Excluded were patients with: contra-indications for exercise, mental retardation, standard contra-indications for MRI, or a ventricular outflow obstruction (peak Doppler gradient > 60 mm Hg). Since the focus of this study was on parental moderators, and due to the age-range of the selected questionnaires, adolescents and young adults aged 16 and older were excluded.

Randomization

After informed consent had been obtained, patients received an anonymous study code and were invited for medical and psychological *baseline* assessments. Thereafter, a 'blind' independent researcher allocated the patients to the exercise program or the control group (ratio 2:1) according to stratified randomization. All participants were stratified into groups by age, gender, and cardiac diagnosis. Each first and second patient in the stratification-group (e.g. age-group 10-12, boys, Fontan) was randomized through envelopes. The randomization of the third patient in the stratification-group was dependent of the previous two randomizations.

Intervention

The standardized exercise program consisted of 3 training sessions of 1 hour per week, during a 12-week period. The program consisted of 10 minutes warming-up, 40 minutes aerobic dynamic cardiovascular training (60-70% of heart rate reserve, based on baseline ergometer-test), and 10 minutes cooling down. Children who already participated in other sports activities participated in 2 training sessions per week. The standardized program was performed group-wise, under supervision of a trained physiotherapist in local physiotherapy centres throughout the Netherlands. The same researcher (ND) visited all participating physiothera-

pists prior to the start of the program and visited them thereafter when needed, to ensure standardized implementation of the exercise program. The control group continued their normal daily live and were invited for a baseline and a follow-up medical and psychological assessment.

Assessment procedure

The ethics-committee review boards of all 5 medical centres approved the research protocol. All eligible patients and their parents were approached uniformly through a patient-information letter and completed the same psychological instruments at 2 points in time. The baseline psychological assessment, a *web-based* questionnaire and a semi-structured interview by phone, took place no longer than 2 months before the start of the exercise program, and 1-3 days before the baseline cardiac assessment in the hospital. The second psychological assessment was performed no later than one month after completion of the exercise program, and no more than 2 weeks after the second cardiac assessment in the medical centre. Assessments for control groups were performed at comparable timepoints.

Outcome Measure

The primary outcome measure was the TNO/AZL Child Quality of Life Questionnaire Child Form (TACQOL-CF), a generic instrument that measures self-reported general aspects of HRQoL in children[16]. The TACQOL-CF assesses the occurrence of functional problems, and if such problems occur, subsequently negative emotional reactions are assessed. The TACQOL-CF consists of 6 scales (56 items): 1) pain and physical symptoms, 2) motor functioning, 3) cognitive functioning, 4) social functioning, 5) global positive emotional functioning and 6) global negative emotional functioning. The satisfactory psychometric properties have been described by Verrips[17].

Parental moderators

Parental mental health was assessed with the 28-item Dutch version of the *General Health Questionnaire-28 (GHQ-28)*[18, 19]. The reliability and validity of the Dutch GHQ-28 were satisfactory[19]. The GHQ-28 consists of one total GHQ-score and four scales: somatic symptoms, anxiety/insomnia, social dysfunction, and severe depression. The GHQ normative group consisted of 485 participants from the general population (45% male), aged 18 years and older from the general population[19].

Parental social support for exercise was assessed with the Dutch version of the *Social Support for Diet and Exercise*[20, 21] that consists of 3 scales (18 items). For this study we used one scale: Family support for Exercise Habits Scale: Participation and Involvement (SSE). No normative data for adolescents were available.

Statistical analysis

This randomized controlled trial is designed according to the CONSORT guidelines[22] with analyses conform the intention-to-treat principle. Baseline scores of the TACQOL-CF, GHQ-28, and SSE for participants with follow-up assessment and those lost to follow-up were compared with Mann-Whitney tests ($p<0.05$).

First, correlations between pre-post changes for TACQOL-CF subscales and baseline GHQ-scales and SSE were calculated. Then, we used general linear models, in which the repeated measures of TACQOL-CF baseline and follow-up scales were regressed on time, study group, and parental moderators. We tested moderations of parental variables through interactions of those parental variables with study group[15]. For each TACQOL-CF scale, univariate regressions were tested against a significance of p <0.008 (Bonferroni correction, $p = 0.05/ 6$ parental moderators), then *Beta* with standard error was reported. After this, we calculated correlations between parental moderators to identify collinearity. Finally, and only if parental moderators' cross-correlations were not too high (>.50)[23], all significant moderators of a specific TACQOL-CF scale were combined in a final repeated measures model to control for each of the other significant predictors.

Comparisons with normative groups were calculated using Students' t tests ($p<0.05$). Data were analysed using SPSS version 20.0.

RESULTS

Preliminary Analyses

Fifty-six adolescents were randomized to the exercise group or the control group (see Figure 1). Two adolescents dropped out directly after the baseline assessment. During follow-up, 1 participant was lost. In case of 12 adolescents data were missing on the main outcome; 7 patients refused to fill in questionnaire, for 1 patient the questionnaire was too difficult, or on parental predictor variables (n = 4); the complete cases sample consisted of data on 41 adolescents and their parent.

No differences were found on baseline TACQOL-CF, GHQ-28, and SSE scores between participants with a follow-up assessment and those lost to follow-up.

At baseline, adolescents in the exercise group did not differ from those in the control group as to baseline demographic characteristics, see Table 1, nor on TACQOL-CF-scores. Parents in the exercise group and those in the control group did not differ on GHQ scores and SSE scores on baseline.

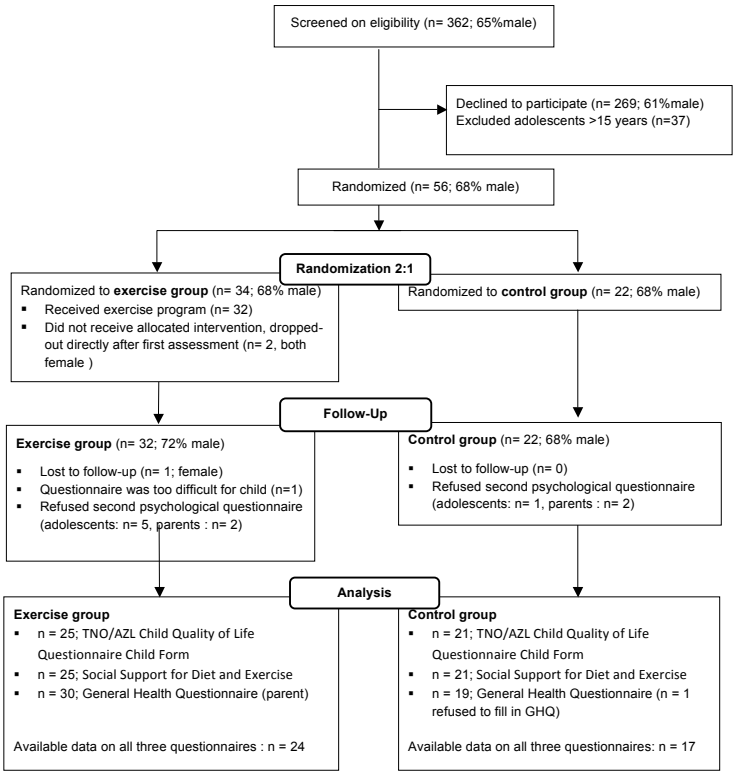

Figure 1: Enrollment in study

Table 1: baseline demographic characteristics

	Exercise group n = 24	Control group n = 17
Child		
Age in years	13.3 (12.0-15.0)	13.2 (11.9-15.3)
Male	17 (70.8)	12 (70.6)
Tetralogy of Fallot	11 (45.8)	7 (41.2)
Fontan circulation	13 (54.2)	10 (58.8)
Parents		
Father	6 (25.0)	5 (29.4)
Age father	46.0 (42.0-49.0)	46.0 (41.8-51.5)
Mother	18 (75.0)	12 (70.6)
Age mother	43.5 (40.3-47.0)	43.5 (41.3-46.8)
Social economic status		
Low (1)	4 (16.7)	1 (5.9)
Middle (2)	7 (29.2)	8 (47.1)
High (3)	13 (54.2)	8 (47.1)

Data are presented as number (percentage), only age is presented as median (inter quartile range)

MODERATING INFLUENCE OF PARENTAL MENTAL HEALTH AND SOCIAL SUPPORT ON HRQOL CHANGES

Parental mental health

Correlations between pre-post changes in TACQOL-CF and baseline parental mental health (GHQ) and parental social support (SSE) scores were divided by exercise group and control group, see Table 2. In the exercise group, six correlations were significant, whereas in the control group no significant correlations were found. In summary, higher parental mental health in the exercise group was associated with less HRQoL changes in adolescents.

In univariate repeated measures analyses, moderations in pre-post changes in TACQOL scales were tested through interactions between parental mental health scales and study group (exercise group versus control group). More parental anxiety/insomnia at baseline was associated with a pre-post decrease in social functioning in the exercise group, compared with the control group, $F(1,37) = 10.5$, $p = .003$. Parental severe depression at baseline and a higher total GHQ score at baseline were also associated with a pre-post decrease in social functioning in the exercise group, compared with the control group (respectively $F(1,37) = 11.8$, $p = 001$ and $F(1,37) = 11.2$, $p = .002$).

According to Cohen's criteria[23], large correlations were found between total GHQ score and anxiety/insomnia $r = 0.71$, $p < .001$, total GHQ score and severe depression, $r = 0.73$, $p < .001$, and severe depressions and anxiety/insomnia, $r = 0.50$, $p < .005$. Therefore, no final model with all significant parental moderators was analysed.

Parental social support for exercise

No significant correlations between changes in child-reported HRQoL and baseline parental social support for exercise were found (see Table 2).

In univariate regressions, no pre-post changes in HRQoL were significantly associated with baseline parental social support for exercise.

Table 2: Correlations between pre-post[1] changes in child-reported health related quality of life, and baseline parental mental health or parental social support

	Baseline General Health Questionnaire										**Social support for exercise**	
	Somatic symptoms		Anxiety/insomnia		Social dysfunction		Severe depression		Total score			
Change in TACQOL-CF	*Exercise*	*Control*	*Exercise*	*Control*	*Exercise*	*Control*	*Exercise*	*Control*	*Exercise*	*Control*	*Exercise*	*Control*
Pain and physical symptoms	-.10	-.05	.25	-.12	.00	-.21	.27	-.01	-.05	-.07	.14	.06
Motor functioning	.23	-.34	-.05	.21	.16	.16	-.08	-.05	.00	.04	.26	.17
Cognitive functioning	-.03	.35	-.07	.21	.05	-.07	-.22	.27	-.66 *	-.09	-.05	.02
Social functioning	-.40	-.18	-.69 *	-.16	-.25	-.08	-.58 *	-.11	-.15	-.05	-.20	.39
Positive emotional functioning	-.37	-.19	-.24	.14	-.43 *	-.41	-.31	-.23	-.59 *	-.20	-.20	.19
Negative emotional functioning	-.41 *	-.23	-.36	-.20	-.15	.12	-.19	-.47	-.39	-.39	-.39	-.21

1. pre-post changes = differences between baseline and follow-up assessment, TACQOL-CF= TNO/AZL Child Quality of Life Questionnaire Child Form, * p< .05

Comparison parental mental health with normative groups

Parental mental health

ConHD-mothers reported less somatic symptoms, anxiety/insomnia, and less symptoms on the total GHQ than normative females, see Table 3. On social dysfunction, they reported more complaints. Further no differences were found, nor for mothers, nor for fathers.

Table 3: gender-specific baseline means of parental mental health and parental social support for exercise

	Mothers (n = 30)	Norm female	Fathers (n = 11)	Norm male
General Health Questionnaire-28 (GHQ-28)				
Somatic symptoms	4.3 (3.3) a	6.7	4.7 (3.0)	5.4
Anxiety/insomnia	3.7 (3.2) a	6.0	5.0 (4.7)	5.5
Social dysfunction	7.5 (1.0) a	6.9	6.8 (0.6)	7.1
Severe depression	1.1 (2.8)	1.6	1.2 (3.3)	1.5
Total score	2.6 (3.6) a	5.5	2.5 (4.6)	3.9
Social support for Exercise (SSE)				
Family support	32.8 (11.3)		30.1 (9.2)	

Data are presented as mean (standard deviation).

GHQ-28; a higher score indicates worse General Health, SSE: a higher scores indicates more social support

a) Significantly different from norm females

DISCUSSION

This is the first study showing that parental mental health moderated the effect of a 12-week standardized exercise program on HRQoL in adolescents with ToF or a Fontan circulation. Compared with controls, adolescents in the exercise group reported a pre-post decrease in social functioning when their parents themselves reported more mental health problems (total GHQ) and more specifically: more parental anxiety/insomnia and severe depression.

Compared with normative females, ConHD-mothers showed similar or even better outcomes on mental health (GHQ). Only on social dysfunction, they reported more complaints. Previous studies into parental mental health have also shown that, on the long-term, parents of somatically ill children reported comparable or even better mental health compared with parents from the general population[24-27]. The phenomenon that parents with a chronically ill child change their internal standards towards their HRQoL is described in previous studies as response shift or post-traumatic growth[28, 29]. Since mothers filled in most questionnaires in our study, it was not possible to compare the small sample of fathers in our sample adequately with those from the general population.

Although parents in our sample reported better mental health than normative groups, adolescents whose parents' overall mental health was worse, reported a pre-post decrease in social functioning after the exercise program, compared with controls. They also reported a pre-post decrease in social functioning when their parents had worse outcomes on severe depression and anxiety/insomnia. Social functioning was assessed as interaction with peers containing the following items: being able to play or talk happily with other children, being able to stand up for myself with other children, other children asked me to play with them, and I felt at ease with other children. An aim of the group-wise exercise program was also to improve social functioning. Parental mental health problems may hamper the expected improvements, or may even establish a decrease, in the social aspect of the group-wise exercise program.

Overall, parental moderators had an influence only on psychosocial HRQoL. Majnemer et al.[30] also found that higher levels of parental stress were associated with lower psychosocial well-being in their child. Furthermore, parental stress and parental psychopathology were also associated with poorer child-reported behavioural and social adjustment[31] and both physical and psychosocial HRQoL[32] in paediatric cancer survivors. In our study, parental moderators did not predict changes in physical HRQoL subscales. We expect that medical and physical parameters will predict changes in physical HRQoL better[30, 33].

As to the associations between parental social support and child-reported HRQoL, some studies[34, 35] reported positive correlations. In contrast, we found no associations. A possible explanation is that the two other studies assessed parent-reported social support, whereas we assessed social support for exercise reported by the adolescents themselves. Moreover, the other studies assessed generic social support, whereas we used a specific questionnaire aimed at family support for exercise habits, sports participation and involvement.

Limitations

Though our RCT-sample is large for this field in research, for statistical analysis it is relatively small, this may have increased type 2 errors. Moreover, selection bias, such as sampling bias, may have occurred. 26% of the eligible adolescents with ToF or a Fontan circulation participated in our RCT.

Clinical implications

This is the first study showing that parental mental health is a significant moderator for effects of an exercise program on HRQoL in their children. Thus, this factor should be taken into account and targeted in clinical practice. Clinicians should communicate and propagate physical activity information and knowledge[36] with depressed and anxious parents in a sensitive way. For parents with mental health problems, it is important that adequate help and, if needed, referral is arranged.

Considering our findings, this may have a beneficial influence on HRQoL outcomes of adolescents taking part in an exercise program.

Conclusions

Adolescents with ToF or a Fontan circulation with parents who showed more severe depression and anxiety/insomnia, or who had poorer overall mental health, showed a pre-post decrease in social functioning after an exercise program. This is the first study showing that parental mental health is a significant moderator for psychological success of an exercise program.

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Chapter 7

General Discussion

GENERAL DISCUSSION

The aim of the present thesis was to investigate the effects of a standardized exercise program on health related quality of life (HRQoL) and psychosocial functioning in children, adolescents, and young adults, aged 10 – 25 years, with tetralogy of Fallot (ToF) or with a Fontan circulation. In addition, the moderating influence of parental mental health and parental social support for exercise on changes in HRQoL after the exercise program was analysed.

Effects of an exercise program on health related quality of life

Children and adolescents with ConHD, aged 10 – 15, who participated in a standardized 12-week exercise program, improved on self-reported subjective cognitive functioning; they experienced less difficulties regarding math, writing, reading, and learning. In a review of studies performed in general population samples, children who were more physically active and more fit obtained better scores as to academic achievement and cognitive functioning compared with those who were not. However, these findings were not supported by intervention studies in healthy children[1], whereas our study indicates a positive effect of an exercise program on self-reported cognitive functioning in youngster with complex ConHD.

Parents of children and adolescents with ConHD, aged 10 – 15, in our sample, reported better social functioning in their child after the exercise program. Since previous studies[2] barely found associations between exercise capacity and psychosocial domains of HRQoL, the improvement on parent-reported social functioning in our sample may be the result of the social nature of the group-wise exercise program. In a systematic review, Eime et al.[3] also found that children and adolescents from the general population, who participated in team sports obtained higher scores as to social functioning, compared with those who did not participate in team sports. Improvement in social functioning is especially relevant, since several studies found elevated levels of social problems and social withdrawal in children and adolescents with ConHD[4-6].

Since many studies reported positive associations between exercise capacity and physical domains of HRQoL[2], we would have expected to find improvements in physical HRQoL domains (pain and physical symptoms and motor functioning) after participation in an exercise program. Surprisingly, this was not the case. This lack of improvements in physical HRQoL in our study could be explained by a ceiling effect on the HRQoL instruments. At baseline, a majority of our sample obtained highest possible HRQoL scores; they scored even higher than normative data. For this majority, it was impossible to improve on physical HRQoL domains. In the minority of children and adolescents with low baseline HRQoL scores, those enrolled in the exercise group improved as to self-reported motor functioning whereas those enrolled in the control group did not.

Overall, our findings are in contrast with outcomes of three smaller, non-randomized studies[7-9]. The intervention study of Rhodes et al.[7] used a comparable exercise program of 12 weeks. They found clinically meaningful improvements on several self-reported health status scales at 1-year follow-up. We found no such improvements in our sample directly after the intervention, i.e. at 12-weeks follow-up. This lack of self-reported improvements in our sample could be explained by the fact that we used a different design and different assessment instruments. Rhodes et al. used voluntary controls, whereas our participants were allocated in a randomized manner. Furthermore, they used a subjective health status instrument (Child Health Questionnaire) whereas we used a HRQoL instrument. Furthermore, Rhodes et al. found improvements at a second follow-up (i.e. at 1 year follow-up). Unfortunately, a second follow-up is missing in our study. Possibly, such a longer-term 1-year follow-up could have unravelled comparable 'sleeper' effects of our exercise program[7].

As to parent–reported improvements, Rhodes et al. did not find health status improvements in children with ConHD after an exercise program, according to the parents[7]. In contrast, we found improvements as to parent-reported social functioning.

Two other intervention studies[8, 9] reported improvements on several subjective health status domains, using the Child Health Questionnaire. Since their intervention comprised a 3-days sports camp and since they assessed subjective health status whereas we assessed HRQoL, their findings were difficult to compare with our results.

In our study, adolescents and young adults with ConHD, aged 16 – 25, did not improve their HRQoL, as assessed with both a generic and a disease-specific instrument, after an exercise program. This lack of improvement may be explained by a ceiling effect. Most adolescents and young adults reported best possible subjective health status scores on the generic SF-36. Remarkably, they scored even better than healthy peers. This ceiling effect could be the result of sampling bias; maybe only those adolescents and young-adults with good HRQoL were motivated to participate in our RCT. The lack of improvement in HRQoL may also be the result of the small sample size of this group of adolescents and young-adults.

On the other hand, the lack of improvements in HRQoL after an exercise program in our sample can also be explained by the nature of the exercise program. This 12-week, 3 times per week, exercise program with a physiotherapist may not be tailored enough to the needs of these adolescents and young adults. A more age-appropriate exercise program, with more focus on obtaining autonomy and belonging to a peer-group, involving more 'normal' sports-participation with healthy peers, might have given better results.

Effects of an exercise program on psychosocial functioning

Emotional and behavioural problems

In our sample of children and adolescents with ToF or with a Fontan circulation, aged 10 – 17, an exercise program had no effect on the level of emotional and behavioural problems. In line, the only previous *intervention*-study that assessed emotional and behavioural problems[10], neither found an effect on self-reported emotional and behavioural problems. In contrast to our findings, their intervention had a positive effect on parent-reported internalizing problems regarding their child. This finding is difficult to compare with ours, since the previous study was non-randomized. Moreover, their intervention comprised two different exercise programs. Finally, their outcomes in the intervention group were compared with those of voluntary controls that did not want to participate in an exercise program.

Although, in our study, participation in an exercise program had no effect on generically assessed internalizing problems, it did decrease self-reported anxiety for sports in children and adolescents with ConHD within the exercise group. Therefore we think that the generic questionnaires, the CBCL and YSR, may not have been sensitive enough to assess (disease specific) changes in emotional and behavioural problems in children and adolescents with ConHD. Besides, possibly as a result of sampling bias and/or the modest response rate, our patients and their parents reported less emotional and behavioural problems at baseline than normative data, which might have made it more difficult to establish a change.

However, the fact that anxiety for sports decreased in the exercise group in our study is important and clinically relevant. We expect that if anxiety for sports participation decreases during adolescence, presumably this may facilitate participation in sports during (young) adulthood, thereby contributing to a healthy lifestyle. This may reduce the risk for cardiovascular complications.

Remarkably, we found an unexpected effect in adolescents in the control group; these adolescents reported improvements on internalizing problems, whereas those in the exercise group did not. Besides, parents of adolescents in the control group reported the same effect, compared with parents of adolescents in the exercise group. Possibly, adolescents (and their parents) in the control group may have felt relieved that they did not have to participate in an exercise program. In addition, they may have benefited from the extra physical check-ups; they may have felt reassurance, experiencing a sense of extra 'safety'. From literature[11, 12], it seems that psychosocial concerns and needs in these adolescents may be neglected.

Concluding, the interaction with a psychologist, the possibility to express emotions, and the feeling of extra medical safety (getting special medical attention) in our study, may have contributed to the positive findings on internalizing problems. It may have made them feel less anxious and depressed, resulting in improved internalizing problems scores.

Sports enjoyment and leisure time spending

In the general population, sports enjoyment in children and adolescents is associated with physical activity during leisure time spending (LTS)[13]. In our study, an exercise program reduced anxiety for sports. However, it had no effect on sports enjoyment or on self-reported active LTS; i.e. bicycling, walking, and sports participation. An explanation could be that children and adolescents with ConHD see exercise as an instrumental purpose, rather than as fun[14]. An implication of this finding may be that it is important to enlarge the fun part in an exercise program in youngsters with ConHD.

On the other hand, children and adolescents in the exercise group reported a pre-post decrease in passive LTS, i.e. computer usage and watching television. Our findings indicate a lack of association between reducing passive LTS and increasing active LTS. This lack of association between reducing passive LTS and increasing active LTS is also seen in adolescents from the general population[15]. Possibly, children and adolescents in our sample, who had busy school-schemes and other activities, replaced their regular passive LTS with participation in the exercise program.

The lack of improvement in sports enjoyment in children and adolescents with ConHD in our study could also explain the lack of improvement regarding choosing active physical activities during their leisure time. Further research should reveal whether an exercise program aimed more at having fun with friends in a more social environment where physical activity is practiced, would enhance their sports enjoyment. This may indirectly improve their active LTS.

PARENTAL MODERATORS

Since parents of children with ConHD may be anxious towards sports participation in their child[14, 16], we assessed the moderating impact of parental mental health and parental social support regarding exercise on changes in child-reported HRQoL after participation in the exercise program.

Remarkably, parents in our sample reported a comparable or even a better mental health than parents from the general population. Other studies also reported this phenomenon[17-20]. This may be due to 'response shift'[21]; parents with a chronically ill child may have different internal standards towards HRQoL compared with normative data (e.g. worrying less about futilities in life). This may have resulted in better mental health scores.

Despite the favourable parental mental health outcomes in our sample, parental mental health did influence HRQoL changes in their children aged 10 – 15 in the exercise group, compared with those in the control group. Children and adolescents whose parents reported

worse overall mental health (more specifically, more anxiety/insomnia and more severe depression) reported a decrease as to social functioning after the exercise program.

Previous studies into children with ConHD found that parental anxiety negatively influenced physical activity participation in their ConHD child[14, 16]. Parental mental health and parental worries were strong predictors for children's emotional adjustment[22, 23]. In addition, we now found that more parental mental health problems, especially anxiety and depression, may negatively influence the effects of an exercise program on social functioning in children with ConHD.

In our study, parental social support towards exercise at baseline was not associated with changes in child-reported HRQoL after an exercise program. Previous association studies reported positive correlations between parental social support and child-reported HRQoL or health status[24, 25]. This discrepancy in findings may be explained by using different informants reporting on parental social support. Previous studies reported on parent-reported social support, whereas in our study we assessed child-reported social support. In addition, previous studies reported on overall parental social support, in our study we assessed parental social support regarding exercise specifically.

On the other hand, in our study, the lack of influence of baseline parental social support towards exercise may also be attributed to sampling bias. Parents who were already more supportive towards exercise may have motivated their children to participate in this RCT. Therefore, their baseline support for exercise may have been higher than that of other parents of ConHD children.

STRENGTHS AND LIMITATIONS

This study is the first randomized controlled trial in children, adolescents, and young adults with ConHD, using a standardized 12-week exercise program, a control group, and standardized multi-informant assessment instruments. As to our total sample size, 93 (26%) eligible children and adolescents with ToF or a Fontan circulation participated in our RCT, of which 70% is male. Though our sample size is larger than samples used in the few previous studies ($n<52$), it is still relatively small. This may be associated with increased type 2 errors. Moreover, sub-analyses for gender and cardiac diagnoses may have had a lack of power. Besides, our patients were motivated to participate in an exercise program. This may have positively influenced their baseline psychological assessment scores, which is reflected in their comparable or even better baseline scores compared with normative data. Due to this ceiling effect, it may have been difficult for children and adolescents to improve their questionnaire scores. Some effects were only found in children and adolescents with low baseline scores, e.g. as to self-reported motor functioning.

Finally, a limitation was that a second longer-term follow-up was not feasible. We expect that a second follow-up might have unravelled sleeper-effects; i.e. long-term effects of the exercise program. Therefore we recommend that future research should include larger samples, and a second, longer-term follow-up assessment.

FUTURE RESEARCH

In our RCT, an exercise program influenced several domains of HRQoL and psychosocial functioning at short term. Since physical activity is important for physical health and HRQoL, essential questions arise, such as:

1. How can we optimize participation in physical activity and exercise programs?
2. How can we attune an exercise program to the individual needs and preferences of children and adolescents with ConHD?

Several factors play a role in these questions, such as*: where, how, by whom*, and *to whom* should an exercise program be given. All these factors clearly warrant future research.

First, how can we optimize participation in physical activity and exercise programs.

Arguments we frequently heard against participation in our RCT were logistic problems of the parents. Moreover, parents also argued that their children already spent a considerable amount of time on school and homework. Therefore, they thought that there was not enough time and energy left to participate in an exercise program. Underlying overprotectiveness and anxiety among parents[14] may perhaps have contributed to these arguments

We think it may be helpful to address realistic and unrealistic attitudes and beliefs of parents towards physical activity and an exercise program in their children. Psycho-education for parents and patients regarding physical activity and an exercise program may solve unanswered questions and (unrealistic) fears and attitudes.

Then, as to the second question: how to attune an exercise program to the individual needs and preferences of children and adolescents with ConHD. We first consider *where* an exercise program should be given. In our multi-centre study, an exercise program was performed under supervision of a physiotherapist in local physiotherapy centres throughout the Netherlands. These centres were near-by the homes of the participants. We consider this as strength of our study.

Secondly, the question *how* should an exercise program be given. We recommend developing more age-appropriate sports-interventions. In this thesis, in children with ConHD, the group-wise exercise program, along with other children with a disability or chronic disease, improved social functioning. However, in adolescents and young adults with ConHD, an exercise program only had an effect on anxiety for sports. Possibly, adolescents with ConHD

may not value an exercise program with only aerobic exercises under supervision of a physiotherapist as a fun leisure activity. Sports enjoyment and having fun in leisure activity are important links between participation and adherence in physical activity[26]. Therefore, an exercise program more tailored to their needs and with a more fun, age-attuned character, may improve the effect of an exercise program on sports enjoyment. For example: participation of a 'best-friend' into the exercise program, or comprising social elements such as dancing into the exercise program. Possibly, including 'game-like' elements (e.g. with electronic, competitive scoring and reinforcements/rewards) may also contribute to a fun character of the exercise program. Such activities may improve their sports enjoyment and influence their participation in physical activity during leisure time.

In addition, as to the question *how* can the content of the exercise program be optimized? Our review into associations between physical outcomes and HRQoL outcomes in children and adolescents with ConHD also indicated an association between self-reported physical limitations and depressive symptoms. Depressive symptoms were also highly associated with self-reported HRQoL. In the general population, a *multicomponent intervention* (a combination of an exercise program with a cognitive behavioural intervention) was effective changing physical activity levels in children and adolescents[27]. In children and adolescents with ConHD, such a multicomponent approach seems especially indicated, since anxieties and concerns (regarding sports) may be present in both adolescents and parents. Possibly, combining an exercise program with e.g. psycho-education, cognitive behavioural techniques, or life style interventions, may also be more effective to change HRQoL and psychosocial functioning.

Thirdly, *by whom* should an exercise program be given? Considering the different physical response to exercise between patients with various diagnoses of ConHD, a physiotherapist who is qualified in exercise in ConHD patients should supervise an exercise program. In our study, the same researcher visited all participating physiotherapists prior to the start of the program, and visited them thereafter when needed, to ensure standardized implementation of the exercise program. We consider this as strength of our study.

Finally, *to whom* should an exercise program be given? Since participation in daily activity and sports commonly is developed during adolescence and may persist into adulthood[28], it is important to stimulate all children and adolescents with ConHD to participate in physical activity and sports. Our exercise program had an effect particularly on children and adolescents with worse baseline HRQoL. Therefore, exercise programs should be attuned especially to this risk group. Furthermore, parental mental health problems influenced the effect of the exercise program on HRQoL changes in children. Parental mental health should also be taken into account and targeted on in future research.

CLINICAL IMPLICATIONS

In general, as stated in the guidelines from the European Society of Cardiology[29], it is recommended for children and adolescents with ConHD to participate in physical activity, in order to improve cardiorespiratory fitness. Participation in physical activity is not only important for physical health, but also for HRQoL[30]. As indicated by our findings, a standardized exercise program improved some HRQoL domains in children and young adolescents, aged 10 – 15, with ToF or a Fontan circulation. Therefore, in line with Takken et al.[29], we recommend children and adolescents with ConHD to daily participate in 60 minutes or more of moderate-to-vigorous physical activity, e.g. recreation sports, active leisure time spending, or an exercise program.

Although our exercise program did not change HRQoL or psychosocial functioning in adolescents and young adults 16 to 25 years, it remains important to motivate these youngsters to participate in physical activity and sports activities. This may have a beneficial influence on their future physical and mental health.

Since especially children and adolescents with low baseline HRQoL scores improved after an exercise program, these children and adolescents should be encouraged to engage in an exercise program programs to improve their HRQoL. To identify children with low HRQoL scores, we recommend integrating semi-structured questions regarding sports participation, anxiety for sports, and depressive symptoms during outpatients' consultations. Patients (and their parents) should be asked, in a structured way, how often they participate in sports, in what kind of sport activities they participate, and if there are any concerns regarding sports participation? Since parental mental health may influence sports participation in their child, this factor should also be taken into account and targeted on in clinical practice. Clinicians should communicate and propagate physical activity information and knowledge with parents in a sensitive way. For parents with mental health problems, it is important that adequate help and, if needed, referral is arranged.

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Appendix 1:

Effects of an exercise program on emotional and behavioural problems in adolescents with tetralogy of Fallot or a Fontan circulation; A randomized controlled trial

Karolijn Dulfer, Nienke Duppen, Nico A. Blom, Ron T. van Domburg, Willem A. Helbing, Frank C. Verhulst, Elisabeth M.W.J. Utens

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In order to improve fitness and physical activity, youngsters with congenital heart disease (ConHD) are encouraged to participate in an exercise program[1]. The effects of an exercise program on behavioural and emotional functioning in these adolescents, however, are still unclear.

Adolescents with ConHD are at an increased risk for behavioural and emotional problems and psychopathology. More specifically, they showed more internalizing problems (anxiety/depression/withdrawn behaviour) compared with healthy peers[2]. An exercise program may contribute to reducing these problems, since physical activity may reduce anxiety and depression[3]. Only four non-randomized studies have been performed in ConHD youngsters, showing positive results of an exercise program on parent-reported emotional, behavioural, and physical functioning[4-7]. On self-reports, however, no significant effects were found. Unfortunately, these previous studies shared methodological problems: small sample sizes, low response rates, different intervention contents, no standardized assessment procedures, and no proper control-groups.

To our knowledge, the present longitudinal, multicenter study is *the first* randomized controlled trial (RCT) into the effects of a standardized exercise program on behavioural and emotional problems. This RCT was performed in a relatively large sample of youngsters with either tetralogy of Fallot (ToF) or a Fontan circulation. We hypothesized that an exercise program would improve the levels of behavioural and emotional problems in these adolescents.

This RCT was conducted to conform to the CONSORT guidelines. The research protocol was approved by the ethics-committee review boards of all 5 medical centres and complies with the 1975 Declaration of Helsinki. All enrolled patients signed an informed consent before participating. For details regarding methods (inclusion, randomization, and exercise program), see Dulfer et al.[8].

Psychological assessment was completed at baseline and at 3-months follow-up. It consisted of a semi-structured interview by phone (assessing biographical characteristics) and a web-based questionnaire measuring: behavioural and emotional problems (*Child Behavior Checklist*[9] and *Youth Self Report*[9]) and anxiety for sports (*Anxiety thermometer*[10], which was specifically designed for this study). The exercise program consisted of 3 training sessions, of 1 hour per week, with group-wise dynamic aerobic training, such as brisk walking/jogging/running/bicycle exercises and dynamic play. Participants were given a heart rate monitor and were instructed to perform their exercises within the given heart range; resting heart rate plus 60-70 % of their heart rate reserve.

Between January 2010 and August 2012, 362 eligible patients were contacted, of which 93 (26%) finally participated[8]. Due to the age-range (10 to 17 years) of the questionnaires, our sample consisted of 71 participants (see Chapter 4, Figure 1). No differences between the exercise-group and control-group were found on demographical characteristics, on baseline emotional and behavioural problems, on baseline cardio-respiratory fitness, nor on baseline participation in sports activities (see Table 1).

Table 1: baseline demographic characteristics

	Exercise group n=42	Control group n=29
Demographic status		
Age in years	14.0 (12.1 - 15.7)	14.9 (12.7 - 16.0)
Male	30 (71.4)	20 (69.0)
Congenital heart disease		
Tetralogy of Fallot	20 (48)	14 (48)
Age at ToF operation	0.5 (0.3 -0.8)	0.7 (0.5 – 1.0)
Fontan circulation	22 (52)	15 (52)
Age at Fontan completion	2.9 (2.5 – 4.0)	3.0 (2.4 – 4.3)
Social economic status		
Low (1)	5 (12)	3 (10)
Middle (2)	16 (38)	12 (42)
High (3)	20 (48)	13 (45)
Missing	1 (2)	1 (3)
Cardio- respiratory fitness		
*PeakVO_2 (% predicted)**	79.8 (16.0)	81.8 (18.7)
Peak load (Watt)	126.4 (44.5)	139.7 (46.5)
Peak heart rate (bpm)	169.5 (21.5)	176.5 (16.1)
VE/VCO_2 slope	29.0 (5.3)	30.2 (7.4)
Participation in sports activities		
Never	4 (10)	3 (10)
1-4 hpw	26 (62)	15 (52)
>5 hpw	12 (29)	11 (38)

Demographic status and participation in sports activities: data are presented as number (percentage), age is presented as median (inter quartile range).

Cardio-respiratory fitness: data are presented as mean (standard deviation).

* n = 9 missing values due to unsuccessful cardiopulmonary exercise test (respiratory exchange ratio (RER) < 1.0.)

Hpw = hours per week, bpm = beats per minute.

The main finding of this RCT was that a 12-week standardized exercise program, overall, had no effect on emotional and behavioural problems in adolescents with ToF or a Fontan circulation (see Table 2). Our findings are in contrast with the more positive outcomes of the few smaller, non-randomized studies in the field[4-7]. The only previous *intervention*-study[4] neither found an effect of an exercise program on self-reports. However, in contrast with our study, parents reported a decrease in internalizing, withdrawn/depressed problems and somatic complaints in their ConHD child. This previous study, however, included only those adolescents who reported their physical fitness to be equal or poorer than healthy peers. Besides, these researchers enrolled varying diagnoses of ConHD, used voluntary controls, and analysed outcomes of two exercise programs together. Three other studies[5-7], showing positive effects of an exercise program on emotional and behavioural domains, are difficult

Table 2: Child Behaviour Checklist and Youth Self Report mean scores

	Child Behaviour Checklist						Youth Self-Report					
	Exercise group (n=37)		Control group (n=26)		p value		Exercise group (n=35)		Control group (n=24)		p value	
Scales	Baseline	Follow-up	Baseline	Follow-up	Δexercise versus Δcontrol	Effect-size	Baseline	Follow-up	Baseline	Follow-up	Δexercise versus Δcontrol	Effect-size
Anxious/Depressed	2.5 (2.4)	2.2 (2.4)	2.7 (3.4)	1.3 (2.5) [c]	0.06	.24	2.9 (3.0)	2.8 (2.7)	3.3 (3.9)	2.4 (3.4)	0.24	.16
Withdrawn/Depressed	2.6 (2.3)	2.3 (2.3)	2.0 (1.9)	1.5 (1.7)	0.57	.07	2.3 (1.9)	2.3 (2.5)	2.7 (2.1)	1.5 (1.8) [c]	0.05 [a]	.26
Somatic Complaints	2.5 (2.0)	2.4 (2.7)	3.2 (1.7)	2.0 (1.9) [c]	0.03 [a]	.28	3.0 (2.1)	2.3 (2.6) [b]	3.4 (2.6)	2.4 (2.2) [c]	0.61	.07
Social Problems	2.9 (2.2)	2.8 (2.8)	2.0 (2.9)	1.7 (2.9)	0.51	.08	3.9 (3.0)	2.7 (2.9) [b]	3.4 (3.0)	2.5 (2.8) [c]	0.79	.04
Thought Problems	2.2 (2.5)	1.9 (2.2)	2.0 (2.6)	1.7 (2.4)	0.92	.01	2.9 (2.5)	2.9 (2.8)	2.8 (2.3)	2.3 (2.4)	0.56	.08
Attention Problems	5.6 (3.1)	4.8 (2.9)	4.7 (4.1)	4.6 (3.7)	0.28	.14	5.1 (3.0)	5.0 (3.2)	5.3 (3.6)	4.7 (3.7)	0.54	.08
Rule-Breaking Behaviour	1.2 (1.3)	1.0 (1.5)	1.8 (1.8)	1.6 (1.5)	0.84	.03	2.7 (1.8)	2.7 (2.7)	3.2 (3.0)	2.5 (2.5)	0.26	.15
Aggressive behaviour	3.6 (3.6)	3.0 (3.7)	4.4 (3.6)	3.9 (4.0)	0.94	.00	3.7 (3.1)	3.2 (3.8)	5.0 (3.5)	3.8 (3.4)	0.38	.12
Internalizing	7.6 (5.0)	6.9 (6.3)	7.9 (5.6)	4.9 (4.7) c	0.04 [a]	.26	8.3 (5.7)	7.3 (6.4)	9.3 (7.6)	6.3 (5.2) [c]	0.09	.22
Externalizing	4.8 (4.6)	4.0 (5.1)	6.2 (4.7)	5.5 (5.2)	0.99	.00	6.4 (4.3)	5.9 (5.8)	8.2 (5.6)	6.3 (5.2)	0.27	.15
Total Problems	26.8 (14.0)	23.1 (16.8)	25.7 (16.4)	21.0 (17.0)	0.71	.05	30.3 (16.1)	26.9 (19.7)	32.7 (17.9)	25.0 (17.3) [c]	0.26	.15

Data are presented as mean (standard deviation), a) Significant pre-post change (Δ) in exercise group versus control group; $p<0.05$, b) Significant change from pre-to-post within exercise group; $p<0.05$, c) Significant change from pre-to-post within control group; $p<0.05$. Effect size (ES) for each pre-post change (Δ) was calculated.

Statistical analyses were on intention-to-treat principle: pre-post changes (Δ) in the exercise group vs. control group with multivariate analysis of variance repeated measures test, changes within each group with paired-sample-t-tests.

to compare with our study. Their exercise program was different; they used non-randomized control groups and completely different assessment moments. Besides, health status was assessed, and not specifically emotional and behavioural problems.

Surprisingly, in our study, the control-group improved on internalizing problems, whereas the exercise-group did not (see Table 2). Specifically, control-patients reported a pre-post improvement on withdrawn/depressive problems ($p<.05$, $ES = .27$), and their parents reported pre-post improvements on internalizing problems ($p<.05$, $ES = .26$) plus somatic complaints ($p < .05$, $ES = .28$). These remarkable improvements of the control group may be attributed mainly to results of the (especially older) girls (see Figure 1). In the general population, girls get less physically active when they enter adolescence, whereas boys do not. Girls in the control-group possibly felt relieved that they did not have to exercise. Besides, they may have obtained a feeling of "safety" and reassurance, receiving two physical and psychosocial examinations. This "special care and attention gave them the possibility to express their emotions, which is especially preferred by girls[11]. Possibly, this may have reduced internalizing problems.

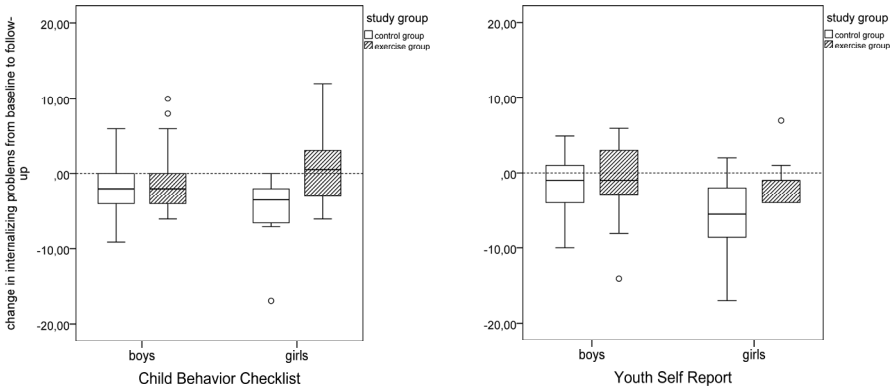

Figure 1: Change from baseline to follow-up in internalizing problems in exercise group and control group, split for gender

As to anxiety for sports, no significant pre-post changes between the exercise-group and control-group were found. However, adolescents *within* the exercise-group reported less anxiety for sports at follow-up ($t(40)=-2.37$, $p<.05$, $ES = .35$), whereas adolescents *within* the control-group did not.

Strength of our multi-centre study is that we used a relatively large sample, a randomized control-group, and a standardized exercise program. Despite these strengths, our RCT

overall showed few effects of an exercise program. This clearly indicates a need for future research. Another follow-up moment could unravel longer-term "sleeper" effects. Moreover, although adolescents in the exercise-group reported less anxiety for sports at follow-up, the exercise program may have been a burden in effort and time. Besides, girls in the exercise-group possibly felt confronted with their physical limitations, especially since our sample had a baseline peak VO_2 of 80% predicted (see Table 1). Presumably, the content, intensity, and duration of the exercise program were not sufficiently attuned to the needs and preferences of the adolescents; future research should focus on how to tailor an exercise program to individual needs.

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Summary

The aim of the present thesis was to investigate the effects of a standardized, 12-week exercise program on health related quality of life (HRQoL) and psychosocial functioning in children, adolescents, and young adults, aged 10 – 25 years, with tetralogy of Fallot (ToF) or with a Fontan circulation. In addition, the moderating influence of parental mental health and parental social support for exercise on pre-post changes in HRQoL was analysed.

In **chapter 1**, the background of the present study was presented. During the last decades, the prognosis of children with congenital heart disease (ConHD) has improved enormously. However, a majority of children need cardiac surgery to survive, with the potential for residua and sequelae. Exercise capacity might be reduced, which may lead to an inactive lifestyle. An inactive lifestyle has been associated with the occurrence of cardiovascular disease, an increased risk of death, and a poorer HRQoL. Therefore, children, adolescents, and young adults with ConHD may benefit from an exercise program. Until now, only a few small, non-randomized studies indicated that participation in an exercise program improved physical outcomes, i.e. exercise capacity and physical activity in children and adolescents with ConHD. On the other hand, effects of an exercise program on *HRQoL* in children and adolescents with ConHD were generally not reported. Furthermore, associations between, on the one hand, physical fitness and exercise programs, and on the other hand, HRQoL and psychosocial functioning in children and adolescents with ConHD, also remained unclear. Therefore, we tried to confirm these positive findings in this randomized controlled trial conducted in 5 participating centres of paediatric cardiology in the Netherlands. We used a larger sample, standardized exercise training, and standardized internationally well-known instruments to assess HRQoL and psychosocial functioning. Overall, 93 patients, aged 10 – 25, with surgical repair for tetralogy of Fallot or with a Fontan circulation for single-ventricle physiology were enrolled. They were randomly allocated, with a ratio of 2:1, to a) the exercise group, with a 12-week program, 3 times per week or b) the control group. Randomization was stratified by age, gender, and cardiac diagnosis. At baseline and follow-up after 12 weeks, all participants completed web-based age-appropriate questionnaires regarding HRQoL and psychosocial functioning

In **chapter 2,** studies into associations between exercise capacity, physical activity, and psychosocial functioning in children with congenital heart disease were systematically reviewed. In most studies, exercise capacity was strongly associated with *physical* domains of quality of life (QoL). In contrast, exercise capacity was almost never associated with psychosocial domains of QoL. Physical activity was rarely associated with physical or psychosocial domains of QoL. Remarkably, self-reported depressive symptoms were associated with both *physical* and *psychosocial* domains of QoL. As to the effect of an exercise program on QoL and psychosocial functioning, only four previous studies were published. These studies found promising results, however they shared methodological limitations.

In **chapter 3**, the effects of an exercise program on health related quality of life in children, adolescents, and young adults aged 10 – 25 years, were investigated. HRQoL in

children and adolescents, aged 10 -15, was assessed with the *TNO/AZL Child Quality of Life Questionnaire Child Form* and *Parent Form*, and with the *Linear analogue scale*. In adolescents and young adults, aged 16 – 25, HRQoL was assessed with the *Congenital Heart Disease-TNO/AZL Adult Quality of Life,* and with the *Linear analogue scale*. In addition, in adolescents and young adults, health status was assessed with the *SF-36 Health Survey*. Compared with the control group, children aged 10 – 15 in the exercise group improved significantly on self-reported cognitive functioning and parent-reported social functioning. Particularly, children in the exercise group with low baseline HRQoL scores reported improvements in both cognitive and motor functioning, whereas those in the control group did not. Youngsters, aged 16 to 25, did not change on HRQoL. Cardiac diagnosis had no influence on pre-post changes in HRQoL. Compared with normative data, our sample reported comparable or better HRQoL at baseline.

In **chapter 4**, the effects of an exercise program on emotional and behavioural problems (*Child Behaviour Checklist* and *Youth Self Report*) and anxiety for sports (*Anxiety thermometer*) were assessed in children and adolescents aged 10 – 17 years. Overall, a standardized exercise program had no effect on psychological problems. From pre-to post assessment, adolescents *within* the exercise group reported a pre-post decrease in anxiety for sports, whereas those *within* the control group did not. Remarkably, adolescents (especially older girls) in the control group and their parents reported improvements as to internalizing problems. Possibly, two medical and psychological examinations may have given them a feeling of 'safety' and reassurance. These contact moments, together with the knowledge that they did not have to exercise three times a week, might have relieved them and made them feel less anxious and depressed. Cardiac diagnosis did not influence the results. Compared with normative data, at follow-up our patients and their parents obtained on almost all scales comparable or better scores.

In **chapter 5**, the effects of an exercise program on sports enjoyment (*Groningen Enjoyment Questionnaire*) and leisure time spending (*Rotterdam Leisure-time Spending Questionnaire*) in children and youngsters aged 10 – 25 were assessed. We also identified the moderating influence of their baseline health behaviour (*Rotterdam Health Behaviour Questionnaire*) and disease knowledge (based on *Leuven Knowledge Questionnaire for Congenital Heart Disease*). At follow-up, the exercise group showed a decrease in passive leisure time spending (watching television and computer usage), compared with controls. On the other hand, an exercise program had no effect on sports enjoyment or on active leisure time spending (sports activities, walking, and cycling). Our sample obtained leisure time spending scores comparable to normative data.

Baseline disease knowledge had a moderating influence on pre-post changes in sports enjoyment. Patients in the exercise group who had knowledge about endocarditis reported more pre-post change in sports enjoyment. Health behaviour (i.e. smoking and drinking alcohol), knowledge about the name of their ConHD did not influence pre-post change

in sports enjoyment nor on leisure time spending. Possibly, this lack of influence could be explained by the low frequencies as to drinking alcohol and smoking in our sample.

In **chapter 6**, the moderating influence of parental mental health (*General Health Questionnaire-28*) and parental social support towards exercise (*Social Support for Diet and Exercise*) on pre-post changes in HRQoL in patients, aged 10 – 15, with ConHD were investigated. Compared with controls, adolescents in the exercise group reported a pre-post decrease in social functioning when their parents reported more mental health problems for themselves, and, more specifically, more parental anxiety/insomnia or severe depression.

Parents in our sample reported comparable or even better mental health for themselves, compared with normative data. Since parental anxiety may hamper participation in physical activity in children with ConHD, this factor should be taken into account and targeted on in clinical practice. Clinicians should communicate and propagate physical activity with depressed or anxious parents in a sensitive way. For parents with mental health problems, it is important that adequate help and, if needed, referral is arranged.

Finally, in **chapter 7,** the main findings and conclusions of this PhD thesis were discussed. Overall, a 12-week standardized exercise program improved self-reported cognitive functioning, and parent-reported social functioning. Furthermore, it resulted in a decrease in passive leisure time spending. In contrast, it had no effect on emotional and behavioural problems, on sports enjoyment, or on active leisure time spending. Parental mental health moderated changes in social functioning: adolescents in the exercise group whose parents' overall mental health was worse, reported a pre-post decrease in social functioning, compared with controls.

This study was the first randomized controlled trial in children, adolescents, and young adults with ConHD, using a standardized 12-week exercise program, a control group, and standardized multi-informant assessment instruments. As to limitations, though our sample was relatively large for this field of research, for analyses the sample was still relatively small, which may be associated with an increased type 2 error. Sub analyses regarding gender and cardiac diagnosis may have had a lack of power. Besides, our sample was motivated to participate in an exercise program, which may have positively influenced their baseline psychological scores. Moreover, a second longer-term follow-up was not feasible. Possibly, such a longer-term second follow-up might have unravelled sleeper effects.

Future research should in our opinion focus on the themes: how to optimize participation in physical activity and exercise programs, and how to tailor an exercise program to the individual needs and preferences of children, adolescents, and young adults with ConHD. Research questions to be answered are: where should an exercise program be given, how should it be given, what should be the content, by whom should it be given, and to whom should it be given. Effects of an exercise program may be improved by participation of a 'best-friend', or by comprising social elements such as dancing. Possibly, including 'game-like' elements (e.g. with electronic, competitive scoring and reinforcements/rewards) may also

contribute to its fun character. Besides, combining an exercise program with e.g. psycho-education, cognitive behavioural techniques, or life style interventions, may also be more effective to change HRQoL and psychosocial functioning.

Clinical implications for medical practice. In line with previous recommendations, children and adolescents with ConHD should participate in 60 minutes or more per day of moderate-to-vigorous physical activity, e.g. recreation sports, active leisure time spending, or an exercise program. Since our RTC showed that especially children and adolescents with low baseline HRQoL scores improved after an exercise program, particularly these patients should be encouraged to engage in an exercise program to improve their HRQoL. To identify children with low HRQoL scores, we recommend integrating semi-structured questions regarding sports participation, anxiety for sports, and depressive symptoms in outpatients' consultations.

Samenvatting

Het doel van dit proefschrift was het onderzoeken van de effecten van een gestandaardiseerd, 12-weken durend inspanningstrainingsprogramma op de gezondheidsgerelateerde kwaliteit van leven (G-KvL) en het psychosociaal functioneren van kinderen, tieners en jongvolwassenen (leeftijd 10 tot 25 jaar) met een tetralogie van Fallot (ToF) of met een Fontan circulatie. Daarnaast werd de modererende invloed van ouderlijke mentale gezondheid en ouderlijke sociale steun voor sport op veranderingen in G-KvL onderzocht.

In **hoofdstuk 1** werd de achtergrond van het huidige onderzoek beschreven. Gedurende de laatste decennia zijn de overlevingskansen voor kinderen met een aangeboren hartafwijking enorm toegenomen. De meerderheid van deze kinderen moet echter een hartoperatie ondergaan om te kunnen overleven. Deze kinderen houden hier mogelijk beperkingen en restverschijnselen aan over, zoals een verminderd inspanningsvermogen. Dit kan weer leiden tot een inactieve levensstijl. Er is een verband tussen een inactieve levensstijl en het ontstaan van hart en vaatziekten, een verhoogd risico op overlijden, en een lagere kwaliteit van leven. Om een meer actieve levensstijl te bevorderen kan het helpen om kinderen, tieners en jongvolwassenen deel te laten nemen aan een inspanningstrainingsprogramma. Tot nu toe zijn er slechts een paar kleine, niet-gerandomiseerde studies in kinderen en tieners met een aangeboren hartafwijking uitgevoerd. Deze studies lieten zien dat fysieke uitkomsten (zoals inspanningsvermogen en dagelijkse fysieke activiteit) verbeterden na deelname aan een inspanningstrainingsprogramma. Echter, de invloed van een inspanningstrainingsprogramma op de *G-KvL* van deze kinderen en tieners met een aangeboren hartafwijking werd over het algemeen niet gerapporteerd. Daarnaast zijn de relaties tussen enerzijds lichamelijke conditie en inspanningstraining, en anderzijds G-KvL en psychosociaal functioneren, ook nog niet duidelijk in kaart gebracht. Daarom hebben wij geprobeerd om de positieve uitkomsten van eerdere studies te bevestigen in dit gerandomiseerd gecontroleerd onderzoek dat plaats vond op kindercardiologische afdelingen van vijf deelnemende universitair medische centra in Nederland. Dit onderzoek werd uitgevoerd bij een grote steekproef, en er werden een gestandaardiseerde inspanningstrainingsprogramma en gestandaardiseerde, internationaal bekende instrumenten om G-KvL en psychosociaal functioneren te meten gebruikt.

Aan het onderzoek deden 93 patiënten (in de leeftijd van 10 tot 25 jaar) mee die een chirurgische ingreep voor ToF of een Fontan procedure voor een éénkamerhart fysiologie hadden ondergaan. Deze patiënten werden gerandomiseerd toegewezen aan a) de trainingsgroep die 12 weken lang, 3 keer per week ging sporten, of b) de controlegroep. De toewijzing gebeurde met een verhouding van respectievelijk 2:1. De randomisatie werd gestratificeerd uitgevoerd aan de hand van leeftijd, geslacht en type hartafwijking. Bij de voormeting en bij de vervolgmeting na 12 weken werd aan alle deelnemers gevraagd om, via internet, leeftijdsspecifieke vragenlijsten in te vullen over hun G-KvL en psychosociaal functioneren.

In **hoofdstuk 2** werden de eerdere studies die associaties beschreven tussen inspanningsvermogen, fysieke activiteit, en psychosociaal functioneren van kinderen met een

aangeboren hartafwijking, systematisch beschreven. Bij de meeste studies was inspanningsvermogen sterk geassocieerd met *fysieke* domeinen van kwaliteit van leven. Inspanningsvermogen was daarentegen bijna nooit geassocieerd met *psychosociale* domeinen van kwaliteit van leven. Fysieke activiteit was zelden geassocieerd met zowel *fysieke* als *psychosociale* domeinen van kwaliteit van leven. Opmerkelijk was dat zelf gerapporteerde depressieve symptomen zowel met fysieke als met psychosociale domeinen van kwaliteit van leven geassocieerd waren. Slechts vier gepubliceerde studies onderzochten het effect van een inspanningstrainingsprogramma op kwaliteit van leven en psychosociaal functioneren. Deze studies lieten veelbelovende resultaten zien, echter ze hadden methodologische beperkingen.

In **hoofdstuk 3** werden de effecten van inspanningstraining op de G-KvL van kinderen, tieners en jongvolwassenen (in de leeftijd van 10 tot 25 jaar) beschreven. G-KvL van kinderen en tieners in de leeftijd van 10 tot 15, werd gemeten met de *TNO/AZL Child Quality of Life Questionnaire*, met de kind- en ouderversie. Daarnaast werd ook de *Linear analogue scale* afgenomen. G-KvL van tieners en jongvolwassenen in de leeftijd van 16 tot 25 jaar, werd gemeten met de *Congenital Heart Disease-TNO/AZL Adult Quality of Life.* Daarnaast vulden zij ook de *Linear analogue scale* en de *SF-36 Health Survey* in.

Vergeleken met jongeren in de controlegroep, gaven de jongeren , tussen de 10 en 15 jaar, in de trainingsgroep aan dat hun cognitief functioneren was verbeterd na inspanningstraining. Hun ouders gaven aan dat de jongeren verbeterd waren op sociaal functioneren. Met name jongeren in de trainingsgroep die op de voormeting een lage G-KvL score behaalden, rapporteerden een verbetering op zowel cognitief als op motorisch functioneren. Jongeren in de controlegroep die op de voormeting een lage G-KvL score behaalden, verbeterden niet op deze schalen. Jongeren tussen de 16 en 25 jaar gaven geen verandering aan in hun G-KvL. Het type hartafwijking had geen invloed op de verandering in G-KvL. Onze steekproef rapporteerde een vergelijkbare, of zelfs een betere G-KvL in vergelijking met norm data.

In **hoofdstuk 4** werden de effecten beschreven van inspanningstraining op emotionele en gedragsproblemen (*Child Behavior Checklist* en *Youth Self-Report*), en op angst voor sporten (*Angst thermometer*) bij kinderen en tieners in de leeftijd van 10 tot 17. De gestandaardiseerde inspanningstraining had geen effect op psychologische problemen. Echter, de tieners *binnen* de trainingsgroep lieten wel een afname zien in angst voor sporten, terwijl de tieners *binnen* de controlegroep geen verbetering lieten zien. Het was opmerkelijk dat tieners (en dan met name de oudere meisjes), én hun ouders, in de controlegroep een verbetering lieten zien wat betreft internaliserende problemen. Mogelijk hebben de twee uitgebreide medische en psychologische onderzoeken hen een gevoel van veiligheid en geruststelling gegeven. Deze contactmomenten, gecombineerd met de kennis dat ze niet drie keer per week hoefden te gaan sporten, kunnen voor hen een opluchting geweest zijn en hebben er mogelijk voor gezorgd dat ze zich minder angstig en depressief voelden. Het type hartaf-

wijking had geen invloed op de resultaten. De deelnemers en hun ouders rapporteerden op alle schalen van de vragenlijsten vergelijkbare of betere scores in vergelijking met norm data.

In **hoofdstuk 5** werden de effecten van inspanningstraining op plezier in bewegen (Groningen Enjoyment Questionnaire) en op vrijetijdsbesteding (Rotterdam Leisure-time Spending Questionnaire) bij kinderen en jongeren (leeftijd 10 – 25 jaar) beschreven. We onderzochten ook de modererende invloed van hun gezondheidsgedrag (Rotterdam Health Behaviour Questionnaire) en hun kennis over hun ziekte (gebaseerd op Leuven Knowledge Questionnaire for Congenital Heart Disease), beide gemeten bij de voormeting. Vergeleken met jongeren in de controlegroep, besteedden de jongeren in de trainingsgroep, na inspanningstraining, minder tijd aan passieve vrijetijdsbesteding (televisie kijken en computer gebruik). Inspanningstraining, daarentegen, had geen effect op plezier in bewegen en op actieve vrijetijdsbesteding (sportactiviteiten, wandelen en fietsen). Onze steekproef behaalde vergelijkbare vrijetijdsbesteding scores als normatieve gegevens.

Kennis van de ziekte, gemeten bij de voormeting, had een modererende invloed op de veranderingen in plezier in bewegen. Patiënten in de trainingsgroep die wisten wat endocarditis inhoudt, rapporteerden meer verandering in plezier in bewegen dan diegene die dat niet wisten. Gezondheidsgedrag (o.a. roken en alcohol gebruik) en het weten van de naam van hun aangeboren hartafwijking hadden geen invloed op veranderingen in plezier in bewegen, noch op vrijetijdsbesteding. Het is mogelijk dat dit gebrek aan invloed mede verklaard kan worden door de lage frequentie van alcohol gebruik en roken in onze steekproef.

In **hoofdstuk 6** werd de modererende invloed beschreven van ouderlijke mentale gezondheid (General Health Questionnaire-28) en ouderlijke sociale steun voor sport (*Social Support for Diet and Exercise*) op veranderingen in G-KvL van kinderen en tieners met een aangeboren hartafwijking (leeftijd 10 tot 15 jaar). Vergeleken met de controlegroep, rapporteerde de trainingsgroep een achteruitgang in hun sociaal functioneren als hun ouders voor zichzelf meer mentale gezondheidsproblemen rapporteerden, en specifieker gezegd: als hun ouders meer angst/slapenloosheid of zware depressieve gevoelens voor zichzelf rapporteerden.

Ouders in onze steekproef rapporteerden vergelijkbare of zelf minder mentale problemen voor zichzelf vergeleken met normatieve gegevens. Omdat ouderlijke angst een negatief effect kan hebben op deelname aan fysieke activiteiten van jongeren met een aangeboren hartafwijking, moet hier mee rekening worden gehouden in de klinische praktijk. Clinici zouden met angstige of depressieve ouders op een sensitieve manier fysieke activiteit moeten bespreken en aanmoedigen. Voor ouders met mentale gezondheidsproblemen is het belangrijk dat adequate hulp, en zo nodig, doorverwijzing wordt geregeld.

Tenslotte werden in **hoofdstuk 7** de belangrijkste uitkomsten en conclusies van deze PhD thesis besproken. Over het algemeen kan geconcludeerd worden dat jongeren na een inspanningstraining-programma een verbetering lieten zien op hun zelf gerapporteerd

cognitief functioneren, en hun ouders rapporteerden een verbetering van het sociaal functioneren van de jongeren. Daarnaast lieten de jongeren in de trainingsgroep een afname zien in hun passieve vrijetijdsbesteding. Inspanningstraining had daarentegen geen effect op emotionele en gedragsproblemen, plezier in bewegen, noch op actieve vrijetijdsbesteding. Ouderlijke mentale gezondheid beïnvloedde veranderingen in sociaal functioneren van de jongeren in de trainingsgroep. Vergeleken met jongeren in de controlegroep, rapporteerden jongeren in de trainingsgroep van wie de ouders een slechtere mentale gezondheid rapporteerden, een afname van hun sociaal functioneren na het inspanningstraining.

Deze thesis beschrijft het eerste gerandomiseerd gecontroleerde onderzoek bij kinderen, tieners en jongvolwassenen met een aangeboren hartafwijking. In dit onderzoek werd gebruik gemaakt van gestandaardiseerde, 12-weekse inspanningstraining, een controlegroep en gestandaardiseerde meetinstrumenten met meerdere informanten. Alhoewel onze steekproef relatief groot was voor dit onderzoeksgebied, was deze relatief klein om te statistische analyses uit te voeren. Hierdoor kan de kans op een type 2 fout zijn toegenomen. Subanalyses voor geslacht en type hartafwijking hebben daarom mogelijk een gebrek aan power gehad. Daarnaast was onze steekproef gemotiveerd om deel te nemen aan inspanningstraining. Dit heeft mogelijk de psychologische scores op de voormeting positief beïnvloed. Verder was een tweede, langere termijn follow-up niet haalbaar. Een langere follow-up zou eventuele 'sleeper' effecten hebben kunnen ontrafelen.

Toekomstig onderzoek zou zich in onze optiek moeten richten op de volgende thema's: hoe kan de deelname aan fysieke activiteit en inspanningstraining verhoogd worden, en hoe kan inspanningstraining afgestemd worden op de individuele behoeften en wensen van kinderen, tieners en jongvolwassenen met een aangeboren hartafwijking. Onderzoeksvragen die hiervoor beantwoord moeten worden zijn: *waar* zou inspanningstraining gegeven moeten worden, *hoe* zou deze gegeven moeten worden, *wat* zou de inhoud moeten zijn, *door wie* zou deze gegeven moeten worden, en *aan wie* zou deze gegeven moeten worden. Het effect van inspanningstraining zou vergroot kunnen worden door de deelname van een beste vriend of vriendin, of door meer sociale elementen aan het programma toe te voegen (zoals dans). Mogelijk kan het toevoegen van game-achtige elementen (bijvoorbeeld competitieve elementen door elektronisch scoren en belonen) ook bijdragen aan een leuker 'fun' karakter van het programma. Daarnaast kan het combineren van inspanningstraining met bijvoorbeeld psycho-educatie, cognitieve gedragstherapie, of levensstijl-interventies ook effectiever zijn om G-KvL en het psychosociaal functioneren te verbeteren.

Klinische implicaties voor de medische praktijk. Overeenkomstig de huidige aanbevelingen raden wij kinderen en tieners met een aangeboren hartafwijking aan om dagelijks 60 minuten deel te nemen aan matige tot intensieve fysieke activiteit, bijvoorbeeld in recreatiesport, actieve vrijetijdsbesteding, of inspanningstraining. Omdat in ons onderzoek vooral kinderen en tieners met een lage G-KvL verbeterden na inspanningstrainingen, bevelen we aan dat vooral deze patiënten zouden moeten worden aangemoedigd om deel te nemen aan in-

spanningstraining. Om deze kinderen en tieners te kunnen identificeren, bevelen we aan om tijdens poliklinische consulten semigestructureerde vragen te stellen over sportdeelname, angst voor sporten, en depressieve symptomen.

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Promoveren is topsport; promoveren vergt vaardigheid, kracht en inzicht, zoals ook in de definitie van sport beschreven. De wetenschap zou moeten zijn als een sportcompetitie; het primaire doel van een sportcompetitie is om volgens de regels te winnen, en niet om esthetische, artistieke of financiële redenen.

In sport is er als eerste natuurlijk het doel (letterlijk of figuurlijk). Dit doel moet bereikt worden binnen een vooraf bepaald tijdsbestek. In deze tijd moet je, soms individueel soms in teamverband, het beste uit jezelf halen. Om het doel te bereiken train je gedurende het seizoen je vaardigheden, begeleid door een trainer. Tijdens een wedstrijd word je ondersteund door een coach en aangemoedigd door het publiek, waarbij de scheidsrechter in de gaten houdt of je je wel aan de spelregels houdt. Tenslotte word je in voor- en tegenspoed gedurende het sportseizoen bijgestaan door je geliefden.

"Keep your dreams alive. Understand to achieve anything requires faith and belief in yourself, vision, hard work, determination, and dedication. Remember all things are possible for those who believe." Gail Devers (1966) former three-time Olympic champion in track and field

De trainer. Mijn trainer gedurende dit sportseizoen: mijn mede-promotor Dr. E.M.W.J. Utens. Lisbeth, je bent een trainer die zelf helemaal niets met sport heeft, maar het wel heel belangrijk vindt voor je hartekindjes. Daarom zet jij altijd je haar schouders er stevig onder, *dè snapt unnen boer mee éénen errem nog wel*. Lisbeth, je hebt me op alle mogelijke manieren bijgestaan gedurende dit sportseizoen. Gaandeweg het seizoen gaf je me steeds meer vertrouwen, zodat ik zelfstandig te werk kon gaan. Dank voor al je begeleiding en eindeloze vertrouwen in mij.

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"Ask not what your teammates can do for you. Ask what you can do for your teammates." Earvin "*Magic" Johnson (1959) basketball player*

De teamleden. Mijn meest directe teamlid Nienke. Meer dan vier jaar lang hebben we intensief samengewerkt. Vanaf het begin was het duidelijk dat we allebei al ervaren (hockey) teamspelers waren. Alhoewel ons onderzoek niet altijd verliep zoals we gehoopt hadden, zetten we toch steeds weer gezamenlijk onze schouders er onder. Zonder jouw inzet in de kliniek zou mijn proefschrift er niet zijn geweest, heel veel dank daarvoor. En als echte teamspeler sta jij, tijdens de promotie plechtigheid, als middenvelder achter mij, terwijl ik als diepe spits de punten zal proberen te maken. Dank dat je mijn paranimf wilt zijn!

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"Winning isn't everything, but wanting to win is." Vince Lombardi (1913 – 1970) football player and coach.

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Sports creates a bond between contemporaries that lasts a lifetime. It also gives your life structure, discipline and a genuine, sincere, pure fulfillment that few other areas of endeavor provide."
Bob Cousy (1928) basketball player

Door sporten heb ik vriendschappen voor het leven gekregen. Alle teamgenootjes van het kampioenen 'wicked' team van Victoria, wat goed dat we elkaar nog regelmatig zien. Daarnaast, mijn andere kampioenen team van Leonidas. Ook wij zien elkaar regelmatig, hoe goed om te zien dat, ondanks de verschillende wegen die we ingeslagen zijn, we toch regelmatig proberen tijd voor elkaar te maken. En na mijn blessure weer nieuwe sporten ontdekt, samen met mijn buurvrouwen.

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'Simpel is het moeilijkst' Johan Cruijff (1947) voormalig profvoetballer en voetbalcoach

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Lieve, mooie, nieuwsgierige, temperamentvolle, sportieve kinderen van me. Zara, Luna en Núria. Dank jullie wel dat jullie zorgen voor afleiding na een dag hard werken. Wat is het geweldig om te zien dat jullie allemaal jullie eigen, unieke karakter hebben. Ook al botst het af en toe soms best aardig, puntje bij paaltje zorgen jullie goed voor elkaar. Ik hoop dat jullie altijd het beste uit je zelf zullen proberen te halen, laat niemand je ooit zeggen dat je iets niet kunt. Proberen kun je altijd!

The best for last; mi dushi Eusebio. Door jouw onvoorwaardelijke steun en liefde heb ik dit alles kunnen bereiken. Dank voor het mooie gezin dat we samen hebben, dank voor je eeuwige vertrouwen in mij, en dank dat je de ellendige winters in Nederland voor me doorstaat. Hoeveel ik van je hou? Je ziet het begin, maar niet het einde….

Curriculum Vitae

Karolijn Dulfer was born on 6th of June, 1978 in Nieuwe-Tonge, the Netherlands. After completing her pre-university education in 1996 at 'Jacob van Liesveldt' in Hellevoetsluis, she started her study Interior Design at 'Willem de Kooning Academy' in Rotterdam. After graduation in 2000, she pursued her studies at 'Leiden University' in the field of Cognitive Psychology. After graduating cum laude in 2004, she was employed as an interior designer at Architecten aan de Maas in Rotterdam. In 2009, Karolijn was admitted to the Ph.D. program of the Department of Child and Adolescent Psychiatry/Psychology of the Erasmus Medical Center in Rotterdam. Her doctoral research, as described in this thesis, was conducted in cooperation with the department of Paediatrics, Division of Cardiology, Erasmus Medical Center.

PhD Portfolio

SUMMARY OF PHD TRAINING AND TEACHING

Name PhD student: Karolijn Dulfer
Erasmus MC Department: Sophia - KJPP
Research School: NIHES

PhD period: 01-09-2009 t/m 24-12-2013
Promotors: prof. dr. F.C. Verhulst, prof. dr. W.A. Helbing
Supervisor: Dr. E.M.W.J. Utens

1. PhD training

	Year	Workload (Hours/ECTS)
General courses		
• CPO mini-course: methodology of patient orientated research and preparation for subsidy application	2010	8 hours
• Regression Analysis for Clinicians	2012	1,9 ECTS
• Biomedical English Writing and Communication	2012	37,5 hours
• Research Integrity	2012	2 ECTS
• Biostatistical Methods I	2012	5,7 ECTS
		Total 11,5 ECTS
Specific courses (e.g. Research school, Medical Training)		
• Basis Kwalificatie Onderwijs: Teach the Teacher	2012	24 hours
• Basis Kwalificatie Onderwijs: Hoorcolleges geven	2012	8 hours
		Total 1 ECTS
Seminars and workshops		
• PhD day 2010: workshops (1: there's no excuse for writing unreadable articles and 2: PhD training at ErasmusMC)	2010	8 hours
• PhD day 2011: workshops (1: expedition to your future and 2: grant application)	2011	8 hours
• NWO talentendag: workshops (1: leidinggeven voor beginners and 2: creatief denken)	2011	8 hours
• Masterclass Nederlandse hartstichting: Aansprekend vertellen over uw onderzoek	2011	4 hours
		Total 1,5 ECTS
Presentations		
• Presentation: Landelijke contactdag PAH	2010	8
• Poster presentation Paediatric Psychology the Netherlands	2011	40
• Presentation: Coeur Research Seminar	2011	8
• Presentation: Combi Treatment/Research meeting Paediatric Psychology ErasmusMC-Sophia	2011/2013	16
• Presentation AEPC Psychosocial Meeting, Cologne, Germany	2013	40
• Poster presentation: Sophia Paediatrics Research day	2013	40
		Total 5,4 ECTS
(Inter)national conferences		
• Generation R symposium, Rotterdam, The Netherlands	2010	8 hours
• AEPC Psychosocial Meeting, Cologne, Germany	2013	2 days
Other		
• Attending several contact days for patients with congenital heart disease		
• Attending and presenting at Research Work Meetings KJP		
• Attending and presenting at Research meetings Paediatric Psychology ErasmusMC-Sophia	2010 •2013	
• Attending and presenting at Quality of Life Meetings ErasmusMC-Sophia		

2. Teaching

	Year	**Workload (Hours/ECTS)**
• Vaardigheidsonderwijs: Normale psychische ontwikkeling van 0 tot 5 jaar	2011/2012/	
• Minor kindergeneeskunde: aangeboren hartafwijkingen	2013	
	2011	
Supervising Master's theses		
• K. Breeman: Health status and quality of life in children and adolescents with congenital heart disease	2010	
Reviewing Master's theses		
• Several medical students from the Erasmus MC – Thorax Center (J.C. Van den Berge, A. Spronk, E.M.J. Hartman, P.R. Robbens)	2012 •2013	

3. Patient care

	Year	**Workload (Hours/ ECTS)**
• Mede-behandelaar Vriendenprogramma	2010 and 2011	

PUBLICATIONS

Dulfer K, Duppen N., Helbing W.A., Utens E.M.W.J. (2013). Associations between exercise capacity, physical activity, and psychosocial functioning in children with congenital heart disease: a systematic review. *European Journal of Preventive Cardiology, 2013 Jun 20, [Epub ahead of print]*

Dulfer K., Duppen N., Blom N.A., Van Dijk A., Helbing W.A., Verhulst F.C., Utens E.M.W.J. (2013). 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. *Congenital Heart Disease*, *2013 Dec 9 [Epub ahead of print]*

Dulfer K., Duppen N., Blom N.A., Helbing W.A., Verhulst F.C., Utens E.M.W.J. (2014). Effects of Exercise Training on Behavioural and Emotional Problems in Adolescents with Tetralogy of Fallot or a Fontan Circulation; A Randomized Controlled Trial. *International Journal of Cardiology, 2014 Jan 11 [Epub ahead of print]*

Dulfer K, Duppen N., Kuipers I.M., Schokking M., Van Domburg R.T., Verhulst F.C., Helbing W.A., Utens E.M.W.J. (2014). Aerobic exercise influences quality of life of children and youngsters with congenital heart disease; a Randomized Controlled Trial. *Journal of Adolescent Health, 2014 Feb 8, [Epub ahead of print]*

Duppen N., Takken T., Hopman M.T., Ten Harkel A.D., **Dulfer K.**, Utens E.M.W.J., Helbing W.A. (2013). Systematic review of the effects of physical exercise training programmes in children and young adults with congenital heart disease. *International Journal of Cardiology, 2013 Oct 3;168(3):1779-87*

Book chapter

Dulfer, K., Helbing W.A., & Utens E.M.W.J. (2012). Coping in Parents of Children with Congenital Heart Disease. In B. Molinelli & V. Grimaldo (Ed.), *Handbook of the Psychology of Coping: New Research* (pp. 307-320). Hauppauge, NY: Nova Science