



PhD thesis

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Rehabilitation in adolescents with congenital heart disease



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Papers included in the thesis

Paper I

Klausen SH, Mikkelsen UR, Hirth A, Wetterslev J, Kjaergaard H, Sondergaard L, et al.

Design and rationale for the PREVAIL study: effect of e-Health individually tailored encouragements to physical exercise on aerobic fitness among adolescents with congenital heart disease--a randomized clinical trial. Am Heart J 2012 Apr;163(4):549-56.

Paper II

Klausen SH, Andersen LL, Sondergaard L, Jakobsen JC, Zoffmann V, Dideriksen K; Kruse A, Mikkelsen UR, Wetterslev J.

Effects of eHealth encouragements to physical activity in adolescents with congenital heart disease: The PReVaiL randomized clinical trial. In review, *International Journal of Clinical Cardiology*

Paper III

Klausen SH, Wetterslev J, Sondergaard L, Andersen LL, Mikkelsen UR, Dideriksen K, et al.

Health-Related Fitness Profiles in Adolescents With Complex Congenital Heart Disease. J Adolesc Health 2015 Jan 30.

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Preface

This thesis is based on the Paediatric Rehabilitation for Vanguard in Life skills Trial/PReVaiL performed during my employment at the Research Unit for Women's and Children's Health, The Juliane Marie Centre, a part of Rigshospitalet, Copenhagen University, in the period 2009 - 2015.

The source of inspiration for this thesis was my clinical work with children and adolescents, who have been so unfortunate to be born with a congenital heart disease. I am continually fascinated by their courage, insights, resilience and capacities to deal with traumatic, unfamiliar and at times life threatening situations.

This project was initiated by my master thesis; The best possible Life in Adolescents with Congenital Heart Disease. In a phenomenological analysis of interviews I found, that the best possible life is associated with the ability to keep wellness in the foreground, and illness in the background. The best possible life is experienced through the body, and is constituted in relation with other people.

I would like to thank all the enthusiastic people who have contributed to the thesis and supported me throughout the process. The research project was initially encouraged by the late Hanne Kjærgaard. Thank you Hanne, you are missed! I would also like to express my gratitude to my supervisors Lars Søndergaard, Jørn Wetterslev, Lars Andersen and Vibeke Zoffmann for constant support, constructive criticism, rewarding discussions and their strive for highest scientific standards. Thanks to the Copenhagen Trial Unit for their consultancy, support and coordination whenever needed, in all stages of the clinical trial, and to Janus Christian Jacobsen for statistical help and co-authoring the final manuscript.

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A warm and special thank goes to Philip Moons and the i-DETACH team from Leuven for your valuable inspiration, attention and hospitality during my three-month stay in 2013, and for co-authoring the “Health related fitness” manuscript.

I am indebted to the test team. Thanks to Susanne Christensen. Your unfailing creativity has qualified the project in every way. Thanks to Martin Kjærsgaard, Gitte Henner Lehmkuhl, Anne Merland Kruse and Kasper Dideriksen, who showed great commitment to this project. Thanks for creating meaningful test days together with patients and their parents, and for good fun and friendship. You have taught me so much.

A strong focus on research and development in The Juliane Marie Centre has developed a resilient research environment, the Research Unit for Women’s and Children’s Health. I owe a warm thank to my past and present colleagues at 7821, who have celebrated and agonized with me over the last years. Thanks for an inspiring and friendly environment. A sincere thanks to the management team of the Julianne Marie Centre, previously Sanne Wilsdahl and Bent Ottesen, and presently Mette Friis and Kurt Stig Jensen for invaluable support over the years.

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The adolescents and their parents participating in this trial are thanked for travelling to Copenhagen from all parts of Denmark. Meeting with you all has been such a pleasure, and I thank you for all your positive remarks and comments along the way.

Finally, I would like to thank my wonderful family and friends. I am grateful for your continuous support, understanding and patience.

Copenhagen, June 2015

List of abbreviations

AM	ante meridiem
ANCOVA	analysis of covariance
BMI	body mass index
CHD	congenital heart disease
FEV1	forced expiratory volume in one minute
GPS	global positioning system
Hg	mercury
HRmax	maximum heart rate
Kg	kilogram(s)
M	metre(s)
MANOVA	multivariate analysis of variance
Min	minute(s)
MI	millilitre(s)
Mm	millimetre(s)
MVPA	moderate to vigorous physical activity
NYHA	New York Heart Association
PedsQL	Paediatric Quality of Life Inventory
PM	post meridiem
RER	respiratory exchange ratio
SMS	short message service
SD	standard deviation
TCPC	total cavopulmonary connection
VO ₂	oxygen uptake
W	watt

Introduction

Cardiac rehabilitation for patients with acquired cardiovascular disease has been a part of routine treatment and care in many places for many years. However, paediatric rehabilitation is an emerging field, and rehabilitation for patients with congenital heart disease (CHD) is not an established routine. Paediatric patients differ from adult patients in several ways. First, they are children and adolescents in a life stage with inherent physical, psychological and social developmental needs. Second, children constantly explore movement patterns, integrating play and fun into the present moment. Third, paediatric patients are utterly dependent on their parents for meeting their needs, including for transportation and commitment to rehabilitation initiatives. Rehabilitation initiatives are often connected to large urban university hospitals and unavailable to children whose parents cannot bring them for exercise training on a regular basis.

Adolescence may be a window of opportunity to rehabilitate patients with congenital heart disease that should not be missed, but it is also a crucial period in life that brings multiple changes and challenges. Adolescents with CHD have a growing desire to be independent and to belong to a peer group, but overprotection by parents may hinder their developing abilities to do both. Consequently, successful paediatric rehabilitation programmes are likely to be directed at developmental needs, involve play and fun, be independent of transportation availability, and involve parents according to the maturity of their child.

eHealth—defined as information and communication technologies for health (1)—is an emerging field within health care that supports an independent lifestyle. This thesis contributes new knowledge about whether cardiac rehabilitation in adolescents with CHD can benefit from adding an eHealth strategy to health education and individual counselling. Cardiac rehabilitation can be defined as exercise with or without education or psychological intervention, delivered to people with heart disease in a hospital, community or home-based setting (2).

Background

Congenital heart disease

The heart is the first organ to form in the embryo (3). CHD is the most frequent congenital disorder and the most frequent cause of infant death from birth defects (4). The reported prevalence of CHD worldwide varies widely across studies, but it has been estimated to be 1.35 million live births each year (5). The overall prevalence of CHD in adults is approximately 3000 per million (6).

CHD can be defined as “a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance” (7, p.324), and encompasses a broad spectrum of cardiac abnormalities. Patients may have more than one defect. The aetiology of CHD is largely unknown, comprising both environmental and genetic components (8). Without treatment, 60% of patients with CHD would die in infancy, 25% in the neonatal period, and only an estimated 15% would survive to adolescence and adulthood. (9) Although CHD has been recognized and documented for many centuries, clinical diagnosis and effective treatments have only become possible within the last 80 years (10). Sixty years ago, the first successful repair of a congenital heart disease was performed using a heart-lung bypass machine (11). Today, more than 85% of all patients are expected to live to adulthood (12). Progress in diagnostic methods, medical and surgical treatments and other invasive techniques have resulted in improved survival rates.

In CHD, prognosis and mortality depend on the type and severity of defect as well as associated abnormalities. Potential late complications are related to e.g. residual lesions, arrhythmia, heart failure, pulmonary hypertension, endocarditis, and thrombo-embolic events (13;14). The majority of patients do not have severe functional limitations. However, patients with CHD have impaired survival compared to the general population (15), and hospital admission rates are twice as high (16). Hospital admissions are most frequently related to endocarditis and heart failure. Based on several studies, two to six persons per 1000 live births are born with a complex or a moderately severe congenital heart disease, and require lifelong specialized follow-up care (17).

Other late complications are related to lifestyle and acquired heart conditions associated with an aging population (18). Arteriosclerotic heart disease originates in childhood, so it is important to address and manage risk factors from an early age (19). Despite its potential to improve long-term prognosis, primary prevention does not seem to be discussed in the paediatric cardiology setting on

a regular basis (20). A study from Belgium found that only 20% of 1071 patients with CHD whose median age was 26 years had a fully heart-healthy lifestyle displaying no risk factors (21). Overweight and obesity are common comorbidities in paediatric CHD (22). A recent longitudinal study found that obese paediatric patients with CHD had 16% lower predicted oxygen consumption and a higher blood pressure response than did patients with CHD and normal weight (23). This might contribute substantially to a future cardiovascular risk factor. There is a need for comprehensive initiatives to meet patients' needs for promoting a heart-healthy lifestyle from an early age.

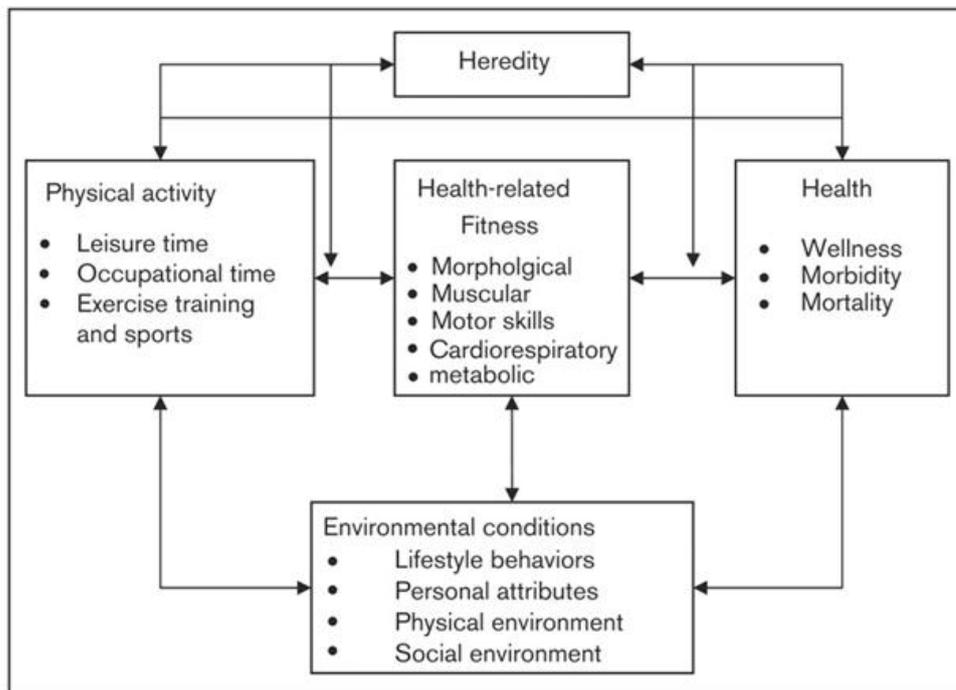
Additional complications and comorbidities of CHD include generalized muscle weakness, which seem to be common (24). Some patients also suffer from impaired motor development (25), neurodevelopmental complications that impact balance and motor skills (26) and scoliosis as a complication of surgery (27). It has also been found that adolescents with CHD are at increased risk of depression and anxiety (28). Reduced exercise capacity is associated with decreased quality of life (29). Thus, habitual physical activity in adolescents should also be encouraged to protect them from comorbidities.

Physical activity

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure (30). Physical activity can be habitual and a part of daily life, as well as part of a structured exercise programme. Physical exercise is defined as a subset of physical activity that is planned, structured and repetitive and has a final or intermediate objective of maintaining or improving physical fitness (30). Physical activity is a complex behaviour that can be described by criteria related to intensity (light, moderate or high) and type (dynamic or static). Physical activity is a positive concept emphasizing social and personal resources as well as physical capabilities (31).

Physical activity is related in a complex way to health, mortality and morbidity outcomes, and it has been suggested that physical activity interacts with health-related fitness (Figure 1) (32). Health-related fitness includes respiratory fitness and is affected by environmental conditions, lifestyle behaviours, personal attributes, the physical and social environment and heredity (33).

Figure 1. Model of relationships between physical activity, fitness and health



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Physical activity can be assessed by self-report or objective measures. However, physical activity is difficult to assess and interpret because no method is completely accurate (34). Consequently, interventions to increase physical activity are also evaluated by health outcomes mediated by physical activity, such as exercise capacity, health-related quality of life and risk markers for metabolic health (35). Among the general adolescent population, higher levels of physical activity are associated with better mental health and reduced risk of obesity and other metabolic and cardiovascular diseases (36). Since physical activity is assumed to be consistent from childhood to adulthood, an active lifestyle should be promoted from an early age (37).

Congenital heart disease and physical activity

The level of physical activity and fitness in adolescents with complex CHD, as compared to healthy adolescents, has been reported to be significantly impaired (38;39). However, results are conflicting in relation to physical activity. (40) Low levels of physical activity may be lifestyle-related in part, because patients with CHD have a potential to improve their physical fitness by physical activity similar to that of their healthy peers (41). Performing regular physical exercise can be challenging for adolescents with CHD, and encouragement to adopt an active lifestyle is needed (42-44). To safely improve physical fitness, physical activity and quality of life, exercise training programmes

in adolescents with CHD have been tested since 1981 (45). Outcomes, inclusion criteria, person-centred care and settings (home-based, facility-based or both) have been monitored in various ways.

Previous studies of paediatric cardiac rehabilitation in CHD

Patient selection

Inclusion criteria vary significantly in previous studies of paediatric cardiac rehabilitation. Until recently most studies recruited patients according to primary diagnosis or type of palliation, e.g., Fontan-type circulation. This may be due to the fact that several recommendations developed for physicians to guide patient participation in physical activity have addressed potential diagnosis-related complications (46;47). However, individualized risk assessments are needed to reduce risks of activities in patients with systolic dysfunction, elevated pulmonary artery pressure, dilatation of the aortae, arrhythmia or central cyanosis. New guidelines address how to evaluate the need for restrictions in type and intensity of physical activity (48). Comparing studies is difficult due to variations in patient inclusion criteria, ranging from patients with severe limitations to those with no limitations to physical activity. Studies including patients with high New York Heart Association (NYHA) class may more readily demonstrate effects due to the poor condition of participants and greater potential to increase cardiorespiratory fitness outcomes. Large variations in age among participants and reported outcomes that are not stratified by gender have the potential to limit the external validity of the results.

Design/ Person-centred care

Person-centred care focuses on the goals, values, and preferences of individuals. Person-centred care is a rapidly developing and growing field within health care, supplementing personalised medicine. (49) Person-centred care is a strategy based on individuals' unique characteristics, rather than a "one-size-fits-all" approach, and takes into account psychosocial needs. It incorporates multidisciplinary approaches and has wide implications for care.

Person-centred care can be directed at both moderators and mediators of physical activity.

Moderators of physical activity in CHD include age, gender and health status. Mediators include perceived competence, self-efficacy, attitude, perceived behavioural control and barriers to physical activity. Self-efficacy has been reported to be both a mediator and a moderator of physical activity in adolescents with CHD.(50;51) Perceived self-efficacy—that one can exercise control over one's health habits—is a core determinant of translating knowledge into effective health behaviours (52)

Uncertainty exists as to how to affect health behaviour and motivate patients to be physically active on a regular basis (53). Therefore, it is important to address mediators and moderators of physical activity in structured rehabilitation interventions.

The effect of including behaviour change theory in exercise training studies in patients with CHD is largely unexplored. Health behaviour is defined as any activity undertaken by an individual, regardless of actual or perceived health status, for the purpose of promoting, protecting or maintaining health, whether or not such behaviour is objectively effective toward that end (31). The use of behaviour change theory may improve the effectiveness of interventions that promote physical activity (54).

Settings / Interventions

The ideal setting for exercise training has yet to be defined for different groups of patients. Facility-based interventions have a potential benefit of increased social support from health care staff and patients; however, transportation may be a problem. Home-based interventions have the potential benefit of social support from family and friends. When distance is a critical factor, eHealth has the potential to deliver health care services as well as social support from healthcare staff in addition to that from family and friends. eHealth is defined as “an emerging field in the intersection of medical informatics, public health and business referring to health services and information delivered or enhanced through the Internet and related technologies” (55, p. 1). It is likely that eHealth interventions will become increasingly important in the delivery of health care, since eHealth has the potential to meet patient demands for information and individual management and care (56). Educational or reminder messages have demonstrated the potential to initiate behaviour change in adolescents and adults (57). There is a need to assess the effects of behaviour change interventions to increase physical activity that can safely and inexpensively connect with adolescents with CHD who reside at a distance from specialist centres, and eHealth may be useful (58). The potential of eHealth—health care delivered or supported through the Internet and related technologies (55)—is largely unexplored, including among patients with CHD. eHealth and person-centred care are foci of the EU Digital Agenda for Health 2020 (59). However, the consequences of adopting these approaches are unknown. Therefore, it is important to test the effectiveness of new initiatives to gain insight and experience with person-centred and eHealth-facilitated rehabilitation programmes in adolescents with CHD.

Outcomes

Increased survival and quality of life are very likely to be meaningful outcomes for patients. These outcomes can only be determined by systematic reviews of rigorous trials. The number of rigorous trials is limited in this field and most studies have used cross-sectional designs, so interpretation of evidence is challenging (60;61). Despite limited evidence supporting the health benefits of physical activity in adolescents with CHD, as well as some modest risks, it has been suggested that physical activity should be encouraged (62). This is mainly due to well-documented lifelong benefits of physical activity on general health, mood and wellbeing (62). This calls for more well-designed randomized controlled trials with predetermined patient-centred outcomes and bias control.

Increased survival has been associated with exercise capacity (63). Only a few studies with the latter as an outcome provide comprehensive reporting of the cardiopulmonary exercise test for assessing the impact of exercise training programmes, and they are difficult to interpret due to missing details about testing protocols and outcome measures (61). Thorough reporting of testing protocols and outcomes determination is essential to comparing trials and identifying the health benefits of physical activity among adolescents with CHD.

Paediatric rehabilitation - a complex intervention

Paediatric cardiac rehabilitation can be considered a complex intervention (64). A complex intervention consists of a number of interacting components, a number of behaviours and a variety of outcomes (64). Key steps in the development and evaluation of complex interventions are: phase 1) identifying the evidence base; phase 2) feasibility/piloting; phase 3) evaluation; and phase 4) implementation (64). In a complex intervention, the intervention content and delivery are standardized, but the form can be adapted, e.g. to perceived individual needs. This is in contrast to a simple intervention, in which all participants are intended to receive the same dose and level of the intervention. The greater the difficulty in precisely defining the active elements of an intervention and how they relate to each other, the greater the likelihood that the intervention is complex (64).

The core components of cardiac rehabilitation in adolescent CHD are lifestyle risk management, individualized exercise prescription and promotion of physical activity (48). However, it has been claimed that effective cardiac rehabilitation incorporates both supervised exercise training and self-care counselling to reduce the negative impact of illness and increase quality of life (65). The optimal study and design of paediatric rehabilitation programmes do not exist (66). Methodological limitations, particularly high risks of systematic error, random error and design errors, have hampered the internal validity of early studies (67-69). Further investigations are needed to elucidate the most effective rehabilitation strategies for adolescents with CHD.

Aims of studies

Our primary aim was to assess the effect of adding a home-based eHealth intervention to health education and individual counselling for adolescents with CHD. Our secondary aim was to use health-related fitness profiles to identify clusters of adolescents with CHD and examine lifestyle behaviour differences between clusters.

Study outline

The present Ph.D. thesis is based on three papers describing the design of the PReVaiL trial, the results of the PReVaiL trial, and the clustering of participants in the PReVaiL trial at baseline.

Paper I is the design and the rationale for the Paediatric Rehabilitation for Vanguard in Life skills Trial/PReVaiL trial, a nationwide, parallel-group, randomized clinical trial assessing the benefits and harms of adding a home-based eHealth intervention to health education and individual counselling for adolescents with CHD.

Paper II is the main trial report, presenting the results on the predefined outcomes of peak oxygen uptake, physical activity and health-related quality of life. Paper I presents exercise protocol feasibility testing and the trial design.

Paper III is a cross-sectional cluster analysis of health-related fitness among the participants in the PReVaiL trial. Differences in lifestyle behaviours were compared between clusters.

Patients

Patients included in the studies were identified from the Danish National Register of Patients and treated at one of the two paediatric cardiology centres in Denmark: Skejby University Hospital, Aarhus, and Rigshospitalet University Hospital, Copenhagen. (Table 1). Patients who had had previous repair for a complex CHD and were assigned to lifelong medical follow up were eligible for randomization. Complexity was defined as "vulnerable to additional acquired co-morbidities that impact both their cardiac and medical care, including hypertension, pulmonary, renal, and myocardial disease, and coronary artery disease" (70 p.1171). Exclusion criteria included both potential compliance issues e.g. mental retardation and syndromes associated with CHD, as well as safety issues e.g. untreated asthma or a systolic blood pressure of >150 mm Hg measured on the right arm on the day of testing. Furthermore, patient health records were manually checked for clinically important comorbidities that could indicate a reason for exclusion. Eligibility was confirmed by each patient's cardiologist.

Table 1. Inclusion and exclusion criteria with ICD-10 codes

Inclusion criteria:

- Corrected or palliated congenital heart disease with allowance for unrestricted exercise (NYHA 1)
- Diagnosis: Q20.0 Truncus arteriosus communis, Q20.1 Transpositio vasorum incompleta, Q20.3 Transpositio vasorum completa, Q20.5 Inversio ventriculorum cordis, Q21.2 Defectus septi atrioventriculorum cordis, Q21.3 Tetralogia Steno-Fallot, Q22.4 Tricusspidalatresia , Q22.5 Anomalia Ebstein, Q23.2 Mitralatresia, Double outlet right ventricle, Q23.3 Hypoplasia ventriculi sinistri cordis syndrome, Q23.3 Hypoplasia ventriculi dextrii cordis syndrome, Q24.4 Stenosis subaortae congenita, Q25.1 Coarctatio aortae, Q25.1 Coarctatio Aortae, Double inlet left ventricle, Q25.3 Stenosis aortae supra-avalvularis, Q25.5 Pulmonalatresia., Successful Total Cavo Pulmonal Connections (TCPC procedure)
- 13- 16 years of age during recruitment period

Exclusion Criteria:

- Mental retardation, or
- Untreated asthma, or
- Syndromes associated with congenital heart disease, or
- A systolic blood pressure >150 mm Hg measured on the right arm at the day of testing led to exclusion, and a request for a second opinion by the cardiologist in charge.

Abbreviations: NYHA, New York Heart Association

Assessment procedures

Details of assessment procedures are outlined in the methods sections of the respective manuscripts: papers I, II and III. The primary assessment procedures are as follows.

The primary outcome, cardiorespiratory fitness/maximal oxygen uptake ($\text{VO}_2 \text{ peak} = \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was assessed by an incremental cardiorespiratory exercise test performed to exhaustion on a bicycle ergometer (Monark Ergonomic 839E, Monark Exercise AB, Sweden) (71), according to guidelines (72;73). After a 10-minute warm-up period, patients followed the incremental protocol starting at 20 watts (W) + 20W/min for girls and 25W + 25W/min for boys until volitional exhaustion.

Patients were encouraged to maintain a cadence above 80 rounds per minute and to continue for as long as possible during the tests; equivalent levels of encouragement were provided during all tests. To avoid any adverse events, patients did not have to meet specific criteria for achieving $\text{VO}_2 \text{ peak}$ during the tests. Instead, they were encouraged to stop when they felt exhausted or experienced adverse symptoms, whichever occurred first. The mean respiratory exchange ratio (RER) achieved during the tests was 1.3 (standard deviation [SD] 0.1; range 1.0–1.61) and the mean maximum heart rate (HR_{max}) achieved was 189 (SD 11.7; range 157–217), following exclusion of an outlier only reaching 102. These results indicate that efforts at or near the maximum were generally achieved; criteria for achievement of peak oxygen uptake are usually considered a combination of volitional exhaustion, HR near maximum, and RER above a certain level, eg. 1.1 (74). The protocol was designed to achieve exhaustion within 6–12 minutes, which was the case for 61 % of patients, with a mean time to exhaustion of 8.3 minutes (SD 1.9; range 4.1 to 13.3 minutes). All tests were performed without adverse events. Peak oxygen uptake ($\text{VO}_2 \text{ peak}$) was defined as the highest value obtained over a five-second averaging interval, using breath-by-breath measures. The use of the term ‘peak’, rather than ‘maximal oxygen consumption’, acknowledges that it was the peak value achieved under the conditions, not necessarily the true maximum, verified by the described criteria.

Before follow-up testing, patients were instructed not to reveal group allocation to the assessors.

Physical activity was assessed objectively using an accelerometer (ActiGraph model 77146, Pensacola, Florida). Patients were asked to wear the monitors, which were set to record at five-second epochs, on the left hip from 6AM to 10PM for two weekend days and four weekdays. (71) Total minutes per day spent in moderate to vigorous physical activity (MVPA) were assessed using 2000 accelerometer cut-point counts per minute as the lower threshold of moderate-intensity activity (36). Recordings of at least one weekend day and one weekday of at least 10 hours were

defined as valid. Days with more than 10 hours of recordings that included periods where the accelerometer was not worn were adjusted to a full day of 14 hours of estimated awake time for this population (75).

Physical activity was also assessed subjectively by an electronic questionnaire validated by the Health Behaviour of School-aged Children survey (76). Acceptable reliability and validity have been reported (77).

Health-related quality of life was assessed by the Danish version of the Paediatric Quality of Life Inventory questionnaire (PedsQI) (Mapi, Lyon, France) for teens aged 13 to 18 years, using the generic and disease-specific versions (78). Good reliability and validity have been reported. (79;80) Adherence to the eHealth intervention was assessed by physical activities registered by users in the mobile phone application. The threshold for adherence was set at registration of physical activities for at least two consecutive weeks. The application also provided tailored feedback if no activity registration occurred.

Health-related fitness, which refers to risk factors that are associated with premature development of disease, was assessed by cardiorespiratory fitness, muscle strength and body composition. (33) Muscle strength was measured as isometric handgrip strength in kilograms (kg) by a North Coast Hydraulic Dynamometer (Procare, Roskilde, Denmark), and the highest of three values was recorded. (81). Body composition was measured by BMI (kg/m^2) and by the sum in millimetres of skin folds at four sites (biceps, triceps, subscapular and suprailiac) (82). Lifestyle behaviors were assessed by an electronic questionnaire validated by the Health Behaviour of School aged Children survey (76), supplemented by modified questions originally developed for parents to adolescents with CHD (83). A web-based process evaluation assessed the acceptability of the intervention to patients and parents.

Study I: The Paediatric Rehabilitation for Vanguard in Life skills Trial/PReVaiL trial

Methods

Design

The Paediatric Rehabilitation for Vanguard in Lifeskills Trial/PReVaiL trial was a nationwide, home-based, parallel group randomized clinical trial conducted in Denmark between May 2010 and May 2013. The trial was approved by the Danish Data protection Agency (2007-58-0015). The Regional Ethics Committee approved the trial protocol (H-1-2010-025), which qualified for registration at Clinical Trials.gov (identifier: NCT01189981). The trial design and statistical analysis plan were published before the end of the trial (71;84).

Randomization was blinded and stratified by known confounders of gender and high/low maximum oxygen uptake at baseline. Patients were centrally randomized 1:1 according to a computer-based random allocation sequence in permuted blocks with varying block sizes of 6, 8, or 10. The block size was unknown to the trial investigators. The intervention drew on an existing and widely used eHealth platform supporting multiple eHealth applications (85).

The complex intervention, Min.Puls.nu, was developed according to the Medical Research Council guidelines by identifying the evidence base through a systematic literature review of interventions to increase physical activity for people with congenital heart disease (phase 1) (64). Further, protocols and outcome measures for exercise testing and training of patients with CHD were scrutinized. A primary pilot and feasibility test was undertaken (phase 2) (71). MinPuls.nu refers to: me, I am an adolescent, my pulse must come up, so I can experience well being now (MyPulse.now).

A group of stakeholders comprising adolescents with complex CHD and exercise therapists and nurses specializing in CHD adapted an existing software tool developed for overweight adolescents for use with adolescents with CHD. The stakeholder group, a cardiologist specialising in CHD and an exercise physiologist tested the feasibility of the application and the website, followed by feasibility testing with one healthy adolescent and six adolescents with CHD (71). A comprehensive orientation was provided to all research assistants and a guide to testing was developed.

The aim of the trial was to assess the effect of adding a home-based eHealth intervention to health education and individual counselling for adolescents with CHD.

Intervention

The nationwide intervention was home-based. All tests were performed at the Institute of Sports Medicine Copenhagen, University Hospital Bispebjerg by the same assessment team members. All patients received the control intervention, which consisted of health education before baseline testing and individual counselling after baseline testing.

The health education comprised opportunities for interactive learning that lasted 45 minutes and involved up to six adolescents of the same gender. The curriculum focused on physical activity and, to a lesser extent, smoking, alcohol, diet and sleep. The goal of health education and individual counselling was to stimulate sources of self-efficacy (ability and skills) in relation to physical activity (86). Self-efficacy, rather than disease severity, was found to be an influential factor in determining whether adolescents with CHD engage in sports or other physical activities (87). Individual counselling was person-centred, lasted 15 minutes and involved parents. The goal was to reinforce patients' ability and skills related to physical activity after baseline tests and to involve parents in action planning. Behaviour change techniques applied in the intervention included information on the benefits of physical activity, goal setting, action planning, barrier identification and problem solving, provision of graded tasks, environmental structuring, facilitation of social comparison, time management and stimulation of future rewards.(88)

Patients randomized to the intervention group received a 52-week Internet, mobile application, and SMS-based programme (eHealth intervention) to improve fitness. To individually tailor the intervention, participants answered several questions when signing up for the e-Health programme, e.g., how do you assess your fitness? Response options were on a 5-point Likert scale from "very good" to "very poor." Physical activity challenges were tailored to beginning, mid and experienced levels of fitness. Tailored feedback was provided based on a predetermined computer algorithm in the e-Health programme.

The eHealth intervention encouraged short-term, high-intensity activities lasting at least 10 minutes as often as possible during the day. The webpage included information about ways to increase physical activity, video spots of well-known athletes demonstrating exercises, a quiz and a physical activity planning tool.

High intensity physical activity was defined as exertion leading to increased heart rate and respiration. The programme adhered to guidelines from the Danish National Board of Health for

healthy adolescents that state: “Be physically active for at least 60 minutes per day. The activity should be of moderate to high intensity and should extend beyond the usual short-term daily activities. If the 60 minutes are divided, each activity should last at least 10 minutes” (89).

Participants received a new challenge every week, e.g., “The challenge this week is that you must run the longest trip you've ever run. Try to see how long you can keep yourself going”. The participants added the number of minutes and type of exercise to a mobile application, and registered the results on a personal homepage <http://www.minpuls.nu/>. For example, a vigorous activity could give three points per minute or 30 points for 10 minutes. Patients were encouraged to strive for 600 points per day. Educational materials, tracking and simulation tools are available. The participant only has access to the personalized webpage. The programme consists of three main approaches: health education, tailored interactive text encouragements, and a personal exercise-planning tool. Figure 2 displays examples of point values per minute of various activities.

Figure 2. Example of point values per minute of exercise



Patients could monitor their physical activity on a personal website and strive to reach activity levels—bronze (105 points), silver (175 points) or gold (350 points)—on a daily basis.

Standardized elements of the intervention included sign-on procedure, health education content, tracking, registration of physical activities and motivational encouragement. Frequency, intensity, time and type of physical activity were determined by participants and were not standardized.

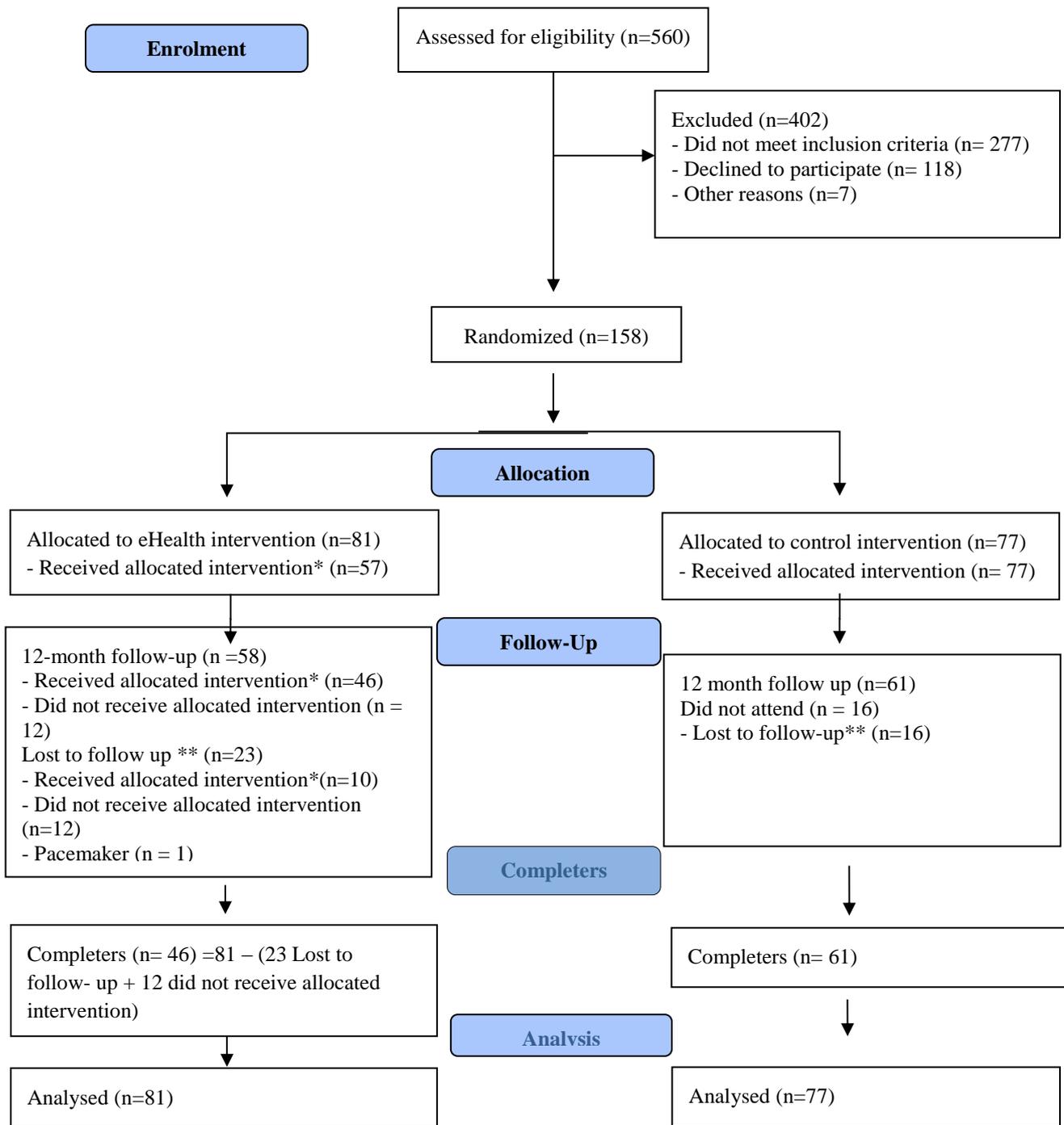
Statistics

Details of the statistical analysis and software are outlined in the methods sections in papers I and II. The main statistical methods are as follows. Sample size was estimated based on previous research among adolescents with CHD (69). Assuming a mean difference of 13W in the cardiorespiratory exercise test between the intervention group and the control group at 12 months, with a standard deviation of 34W, a risk of Type I error (α) of 5% and a risk of Type II error (β) of 20%, we estimated that a total of 216 patients needed to be randomized to the PReVaiL trial. The data were analysed using SPSS version 20.0 and STATA version 13. The statistical analysis plan was published (Clinical trials.gov identifier: NCT01189981) before access to data. Primary analyses for all continuous outcome variables used analysis of covariance (ANCOVA), adjusted for VO₂ peak at baseline and for the stratification variables of gender and high/low exercise capacity. Three populations were analysed: 1) the intention-to-treat population, using multiple imputations for missing data (90;91); 2) the per-protocol population (all patients randomized to the intervention who recorded physical activities to the mobile application in at least two consecutive weeks); and 3) the cluster population. The cluster population was derived from participants randomized in the PReVaiL trial (92). A statistician blinded to group allocation performed all statistical analyses. The authors interpreted the results and formulated the main conclusions of the trial before de-masking the group allocation.

Results

Of 560 patients assessed for eligibility, 283 (51%) met inclusion criteria. Of these, 165 agreed to participate; a total of 158 patients (56%) were randomized, 66 (42%) of whom were girls. The CONSORT diagram appears in Figure 3. Baseline characteristics were similar in intervention and control groups (Table A1). Seventy-five (47%) patients were recruited from Aarhus Skejby University Hospital, and 83 (53%) were recruited from Copenhagen University Hospital Rigshospitalet.

Figure 3. CONSORT diagram



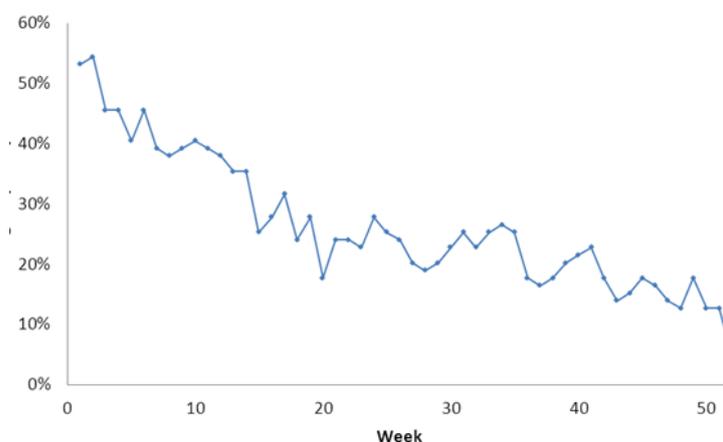
* used the eHealth application for at least 2 consecutive weeks.

** Reasons for becoming lost to follow up included unwillingness to miss school for one day, upcoming exams, loss of interest, and no suitable dates available for appointments.

Adherence to the mobile application

Of 81 patients in the intervention group, just 46 (57%) patients used the eHealth application for at least two consecutive weeks, and completed both exercise tests. 8% of patients were active mobile application users at in week 52 (Figure 4). A total of 24 (30%) patients in the intervention group did not actively use the mobile application for at least two consecutive weeks during the one-year study period and were identified as not adherent to the protocol.

Figure 4. Percentage of active patients throughout the one-year intervention



All *Robust* girls in the cluster population (92), allocated to the eHealth intervention, used the application for at least two consecutive weeks. (Table 2)

Table 2. Numbers of users and non-users in the cluster populations

	Users			Nonusers			Total
	Robust	Moderately robust	Less Robust	Robust	Moderately Robust	Less Robust	
Girls	8	16	2	0	5	4	35
Boys	6	17	8	5	6	4	46

Efficacy of the mobile application

A total of 65 parents (41% of the total sample) and 53 patients (34% of the total sample), of whom 24 were from the intervention group, responded to a web-based process evaluation questionnaire, yielding valuable feedback as well as comments from patients who stopped using the intervention. One patient reported that the mobile application did not allow for retrospective monitoring of activities. Another patient reported being annoyed that several SMS text messages could be delivered in one day.

Patient characteristics

Patient baseline characteristics are presented in Appendix A (Table A1). Mean age was 14.6 years ($SD \pm 1.3$). The most frequent cardiac abnormalities for which patients had had corrective surgery were coarctation of aortae (52, 33%), transposition of the great arteries (35, 22%), and Steno-Fallot tetralogy (21, 13%) (Appendix). The stratification variables of gender and predefined categories of high and low peak oxygen uptake distributed patients similarly between groups. No between-group differences were found at baseline for anthropometrics, lung function or cardiorespiratory fitness. Mean peak oxygen uptake among girls and boys was 37.5 ($SD \pm 8.1$) and 47.9 ($SD \pm 7.9$), respectively. At the time of baseline testing, mean BMI was 21.2 ($SD 3.6$) among girls and 19.5 ($SD 3.0$) among boys.

Active transport to school on most days occurred for 29 (44%) girls and 56 (61%) boys. Most patients, 49 girls (74%) and 79 boys (86%) enjoyed being physically active and 57 girls (86%) and 85 boys (92%) participated in physical education at school most of the time. Nevertheless, 51 (77%) girls and 63 (68%) boys assessed themselves as equally or less physically competent than their peers

Primary outcome

At one year follow up, mean VO₂ peak in the intervention and control groups was 43.2 (SD 9.7) and 46.2 (SD 10.1) ml*kg⁻¹*min⁻¹, respectively (Table 3). In the primary analysis adjusted for baseline VO₂ peak and stratification variables of gender and exercise capacity, the 95% confidence interval (CI) of the between-group difference in mean VO₂ peak included zero and excluded a minimum relevant difference of 3 ml/kg/min. (Table 3). In the fully adjusted analysis, the between-group difference in mean VO₂ peak of -0.41 (95% CI -2.45 to 1.63) (not shown) excluded relevant differences. In the per-protocol population that included all patients randomized to the intervention who recorded physical activities to the mobile application in at least two consecutive weeks, the between-group difference in mean VO₂ peak (not shown) included zero and excluded relevant differences. The subgroup analysis adjusted for cluster allocation yielded similar results (not shown).

Table 3. Between-group differences in maximal oxygen uptake at one year

	Intervention group* n=81		Control group* n=77		Between-group difference** (95 % CI)	P value
	Before	After	Before	After		
VO ₂ peak, mean (SD)	43.7 (9.8)	43.2 (9.7)	43.4 (9.3)	46.2 (10.1)	-0.65 (-2.66 – 1.36)	0.52
Girls	38.5 (7.9)	37.5 (7.4)	36.4 (8.4)	36.6 (7.9)	0.04 (-2.91 – 2.83)	0.98
Boys	47.1 (8.6)	47.8 (9.0)	48.6 (7.3)	50.9 (7.6)	-1.47 (-4.23 – 1.31)	0.30

* unadjusted analyses, **adjusted analyses

Secondary outcomes

Objective measures of physical activity yielded similar results (Table 4), as did subjective measures (not shown).

Table 4. Between-group differences at one year in ≥ 2000 counts per minute per day of moderate to vigorous physical activity

	Intervention group* n=41/81		Control group* n=52/77		Between-group difference**	P value
	Before	After	Before	After		
Physical activity in minutes (SD)	45.8 (24.1)	40.3 (21.8)	49.8 (26.6)	41.3 (22.9)	-.04 (-2.23 - .23)	0.974

* unadjusted analyses, ** adjusted analyses

Exploratory outcome, health-related quality of life

Measures of generic and disease-specific health-related quality of life yielded similar results (Table 5).

Table 5. Between-group differences at one year in mean health-related quality of life score.

	Intervention group* n=81		Control group* n=77		Between-group difference** (95 % CI)	P value
	Before	After	Before	After		
Generic	80.00	80.4	80.4	80.1	0.32 (-2.39 – 3.14)	0.822
Disease-specific	85.21	84.6	84.6	85.6	-.72 (-3.73 – 2.89)	0.637

* unadjusted analyses, **adjusted analyses

Conclusion of the PReVAiL trial

Adding MinPuls.nu, a tailored eHealth intervention, to health education and individual counselling, does not seem to have any effect in adolescents with congenital heart disease. The few experimental participants using the intervention may have contributed to the lack of observed effect. Our results do not support the use of this 52-week Internet, mobile application, and SMS-based programme, delivering individually tailored text messages to encourage physical activity in adolescents with complex congenital heart disease.

Study II: Health-related fitness profiles in adolescents with complex congenital heart disease

Methods

Design

This cross-sectional study was conducted on baseline data from the PReVaiL trial. The aim was to identify common health-related fitness profiles and examine their association with lifestyle behaviours. A cluster analysis allocated randomized patients into profiles, based on health-related fitness variables of cardiorespiratory fitness, body composition and muscle strength.

Statistics

Details of the statistical analysis and software are provided in the methods sections in paper III. The main statistical methods are as follows. A combination of hierarchical and non-hierarchical cluster analysis was used (93). A hierarchical analysis first defined the number of clusters. The agglomeration table produced by SPSS displayed the coefficients of each case and the magnitude of between-case differences, which enabled determination of the optimum number of clusters—in this case, three. When the numbers of clusters was defined, a non-hierarchical analysis was performed. The centroid of each cluster was calculated, and each patient was placed in the cluster with the closest centroid.

Multivariate analysis of variance (MANOVA) analyses were used to detect differences in lifestyle behaviours between clusters. To control for Type I error due to multiple testing, a significance level of .05 after Bonferroni correction was established.

Results

Three distinct profiles were identified (Table 6, Table 7). Profiles were named for the characteristics of the health-related fitness variables forming them. Cluster 1, *Robust*, included 43 patients, 27% of the total sample; this group of very fit and physically strong adolescents included 20 (47%) girls. Cluster 2, *Moderately robust*, included 85 patients, 54 % of the total sample; adolescents in this cluster had a fitness level close to the mean of the total sample and included 37 (42%) girls. Cluster 3, *Less robust*, included 30 patients, 19% of the total sample; these adolescents, characterized by a nonathletic body composition and lack of muscle strength, included 9 (30%) girls. Diagnoses were evenly distributed between clusters (92).

Table 6. Characteristics of adolescent girls across clusters

	Total; mean (SD)	Cluster 1 robust; mean (SD)	Cluster 2 moderately robust; mean (SD)	Cluster 3 less robust; mean (SD)	p values F test
	66	20	37	9	
Age (years)	14.6 (±1.3)	14.3 (1.1)	14.9 (±1.3)	14.0 (±1.2)	.061
Diagnoses [$\chi^2(0,780)$]; n					
TGA	13	4	7	2	
Steno Fallot	9	1	6	2	
CoA	19	8	9	2	
Other	25	7	15	3	
VO ₂ peak	37.5 (±8.1)	42.4 ^a (±7.8)	35.3 ^a (±7.1)	35.7 (±8.9)	.004
HRR	124.1 (±14.2)	129.2 ^b (±11.3)	124.6 (13.5)	106.6 ^b (±12.3)	.006
Oxygen pulse	11.3 (±1.9)	13.2 ^c (±1.5)	10.9 ^c (±1.8)	9.4 ^c (±1.2)	≤.001
Watt max	158.5 (±26.6)	187.7 ^c (±10.3)	153.3 ^c (±12.6)	113.9 ^c (±14.5)	≤.001
Hand grip strength	26.1 (±4.7)	26.7 ^d (±3.4)	27.2 (±4.2)	20.0 ^d (±4.3)	≤.001
BMI	21.2 (±3.6)	21.4 (±3.0)	21.8 (±4.0)	18.8 (±2.5)	.080
Sum of skinfolds	17.8 (±11.1)	15.7 (±8.9)	18.5 (±12.7)	19.3 (±7.4)	.592
RER	1.3 (±.1)	1.3 (±.1)	1.3 (±.1)	1.3 (±.1)	.828
AT	.7 (±.2)	.7 (±.1)	.7 (±.2)	.7 (±.1)	.651

Data are presented as mean (standard deviation) VO₂ peak = ml O₂/kg/min; HRR = heart rate reserve (Max pulse – resting pulse); oxygen pulse = O₂/HR, volume of oxygen consumed by the body per heartheat; Watt max (maximal workload/kg); hand grip strength (kg; body weight); BMI = body mass index (kg/m²); Sum of skinfolds measured at four sites: biceps, triceps, sub scapular, and suprailiac sites; RER = respiratory exchange ratio (the ratio of the amount of carbon dioxide produced to the amount of oxygen consumed or taken up); AT = anaerobic threshold (the exertion level between aerobic and anaerobic training). CoA = coarctation of the aorta; SD = standard deviation; Steno Fallot = Fallot’s tetralogy; TGA = transposition of the great arteries.

Bonferroni post hoc tests include:

^a Significant differences between Cluster 1 and Cluster 2

^b Significant differences between Cluster 1 and Cluster 3

^c Significant differences between Cluster 1, Cluster 2, and Cluster 3

^d Significant differences between Cluster 1 and Cluster 3

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Table 7. Characteristics of adolescent boys across clusters

	Total; mean (SD)	Cluster 1 robust; mean (SD)	Cluster 2 moderately robust; mean (SD)	Cluster 3 less robust; mean (SD)	p values F test
	92	23	48	21	
Age (years)	14.6 (±1.2)	15.6 (±.9)	14.4 (±1.2)	13.8 (±1.0)	<.001
Diagnoses [$\chi^2(0,220)$]; n					
TGA	22	5	12	5	
Steno Fallot	12	2	6	4	
CoA	33	7	22	5	
Other	25	9	8	8	
VO ₂ peak	47.9 (±7.9)	52.3 ^c (±5.5)	48.2 ^d (±7.2)	42.4 ^{c,d} (±8.7)	≤.001
HRR	121.4 (±14.0)	134.6 ^{a,c} (±11.7)	118.1 ^a (±15.5)	114.7 ^c (±15.4)	≤.001
Oxygen pulse	14.2 (±3.7)	18.2 ^b (±3.4)	14.3 ^b (±2.1)	9.8 ^b (±1.4)	≤.001
Watt max	201.7 (±50.1)	267.4 ^b (±24.3)	199.7 ^b (±19.3)	134.5 ^b (±16.7)	≤.001
Hand grip strength	30.3 (±9.4)	40.9 ^b (±7.2)	29.4 ^b (±6.3)	20.9 ^b (±5.3)	≤.001
BMI	19.6 (±3.1)	20.9 ^c (±2.7)	19.8 ^d (±3.4)	17.7 ^{c,d} (±2.3)	.002
Sum of skinfolds	9.5 (±2.1)	10.3 ^c (±2.0)	9.7 ^d (±2.9)	7.9 ^{c,d} (±1.5)	.001
RER	1.3 (±.1)	1.3 (±.1)	1.3 (±.1)	1.3 (±.1)	.532
AT	.7 (±.1)	.7 (±.1)	.7 (±.2)	.7 (±.1)	.210

Data are presented as mean (standard deviation) VO₂ peak = ml O₂/kg/min; HRR = heart rate reserve (Max pulse – resting pulse); oxygen pulse = O₂/HR, volume of oxygen consumed by the body per heartheat; Watt max (maximal workload/kg); hand grip strength (kg; body weight); BMI = body mass index (kg/m²); Sum of skinfolds measured at four sites: biceps, triceps, sub scapular, and suprailiac sites; RER = respiratory exchange ratio (the ratio of the amount of carbon dioxide produced to the amount of oxygen consumed or taken up); AT = anaerobic threshold (the exertion level between aerobic and anaerobic training). CoA = coarctation of the aorta; SD = standard deviation; Steno Fallot = Fallot’s tetralogy; TGA = transposition of the great arteries.

Bonferroni post hoc tests include:

^a Significant differences between Cluster 1 and Cluster 2

^b Significant differences between Cluster 1 and Cluster 3

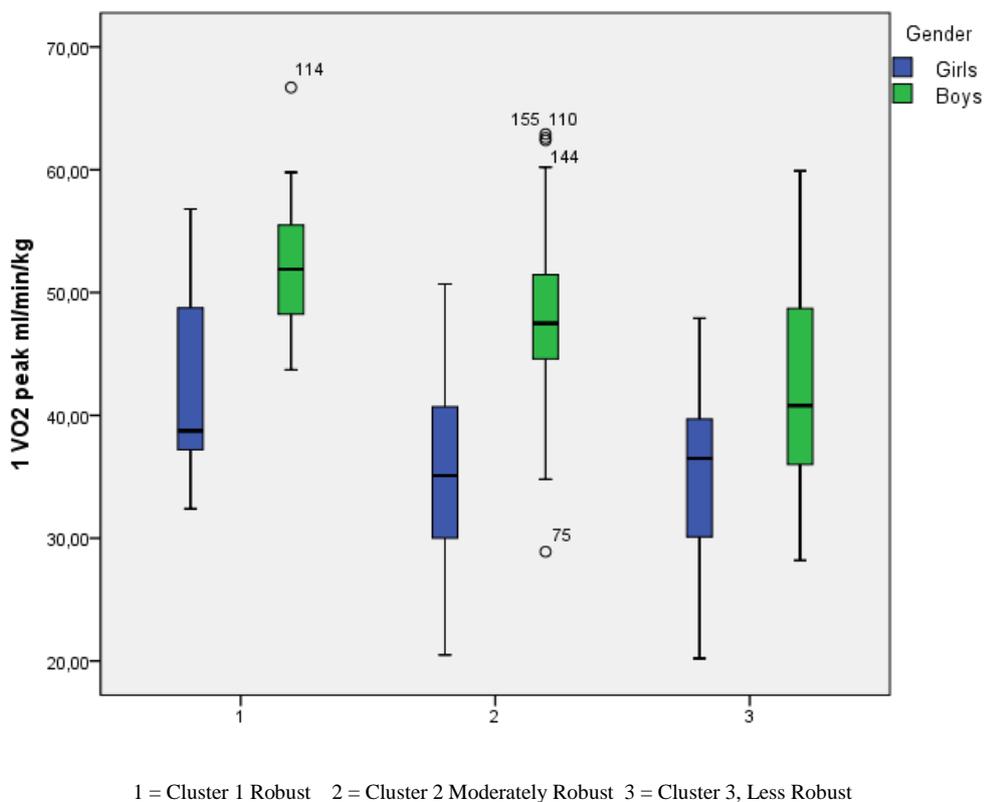
^c Significant differences between Cluster 1, Cluster 2, and Cluster 3

^d Significant differences between Cluster 1 and Cluster 3

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Mean oxygen uptake differed significantly between clusters (Figure 5).

Figure 5. Mean oxygen uptake across clusters

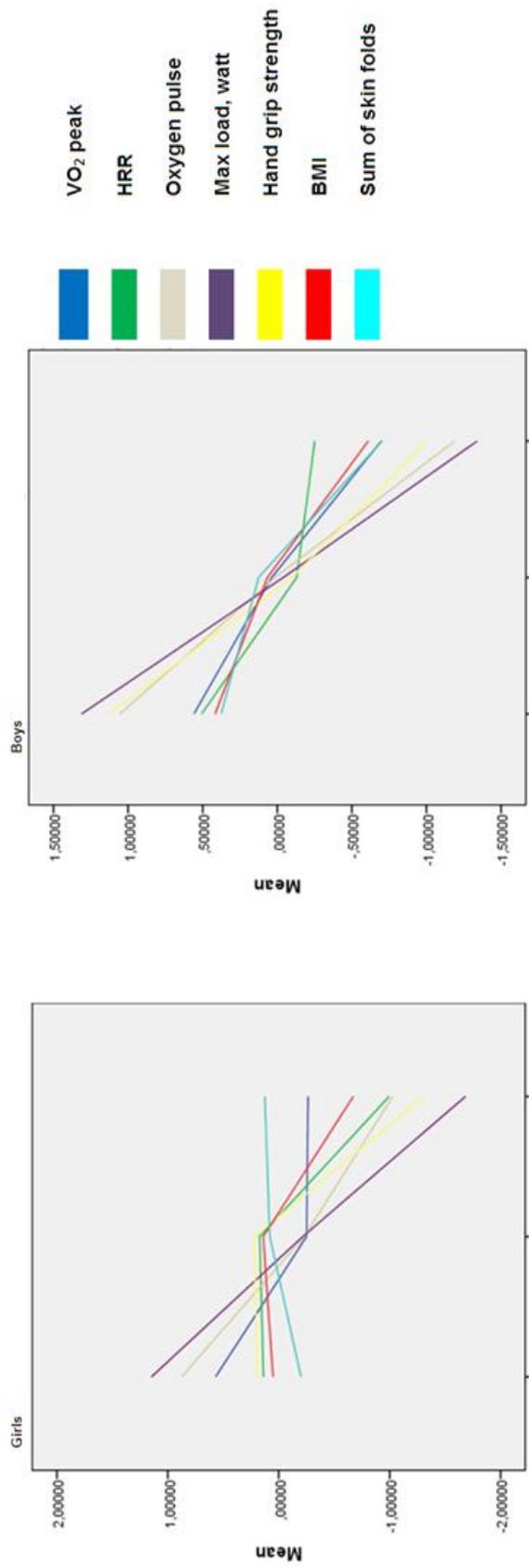


Muscle strength differed between clusters, as did BMI among girls. The girls in the *Less robust* cluster had the lowest BMI among clusters but, paradoxically, the highest sum of skin folds.

Mean z-score values for health-related fitness are presented graphically in Figure 6.

Mean values for lifestyle behaviours are reported in Table 7 and shown graphically by z-scores in Figure 7 and Figure 8. Differences in lifestyle behaviours by gender and cluster are displayed in Table 8.

Figure 6. Mean Z-scores for health-related fitness



1. Robust 2 Moderately Robust 3. Less Robust

1 Robust 2 Moderately Robust 3 Less Robust

Table 8. Mean values for lifestyle behaviours

Variables	Total; mean (\pm standard deviation [SD])	Cluster 1 robust; mean (\pm SD)	Cluster 2 moderate robust; mean (\pm SD)	Cluster 3 less robust; mean (\pm SD)	F	p
Girls						
Self-efficacy	3.2 (.7)	3.4 (.5)	3.2 (.8)	2.9 (.6)	1.525	.226
Exercise-specific self-efficacy	62.3 (32.4)	81.6 (20.7)	54.9 (32.3)	51.4 (38.7)	5.505	.006*
Exercise hours per week	4.3 (1.5)	5.2 (.9)	4.1 (1.4)	2.8 (1.7)	11.037	$\leq .001^*$
Enjoy physical activity	4.1 (1.0)	4.7 (.7)	4.0 (.9)	3.4 (1.2)	6.736	.002*
Physical competence	3.0 (.9)	3.5 (1.0)	2.8 (.8)	2.8 (.9)	3.691	.031*
Self-rated health	3.0 (.8)	3.2 (1.0)	2.9 (.6)	3.0 (.9)	.626	.538
Weekend TV	4.2 (1.5)	4.3 (1.4)	4.3 (1.6)	3.4 (1.7)	1.311	.277
Week days TV	3.2 (1.3)	3.0 (1.2)	3.3 (1.3)	2.9 (1.3)	.416	.661
Feel restricted by heart surgery	1.6 (1.0)	1.3 (.9)	1.6 (.8)	1.9 (1.4)	1.596	.211
Participate in PE at school	4.6 (.8)	4.9 (.3)	4.4 (1.0)	4.7 (.5)	1.675	.196
Boys						
Self-efficacy	3.2 (.6)	3.3 (.5)	3.2 (.5)	3.0 (.6)	.613	.544
Exercise-specific self-efficacy	61.0 (21.0)	66.1 (16.0)	62.2 (21.0)	52.6 (23.6)	2.527	.086
Exercise hours per week	4.4 (1.5)	5.0 (1.4)	4.3 (1.4)	3.9 (1.9)	2.842	.064
Enjoy physical activity	4.2 (1.0)	4.5 (.6)	4.2 (1.0)	3.8 (1.2)	3.256	.043*
Physical competence	3.2 (.9)	3.4 (1.0)	3.2 (.9)	3.0 (.9)	.993	.375
Self-rated health	3.2 (.6)	3.2 (.5)	3.3 (.6)	3.0 (.6)	1.361	.262
Weekend TV	5.3 (1.9)	5.7 (1.9)	5.0 (1.8)	5.4 (2.1)	1.169	.348
Weekdays TV	3.9 (1.7)	3.6 (1.7)	4.0 (1.6)	4.1 (2.0)	.582	.561
Restricted by heart surgery	1.3 (.7)	1.1 (.5)	1.3 (.6)	1.5 (1.0)	1.784	.174
Participate in PE at school	4.6 (.9)	4.8 (.8)	4.6 (.9)	4.5 (.8)	.527	.517

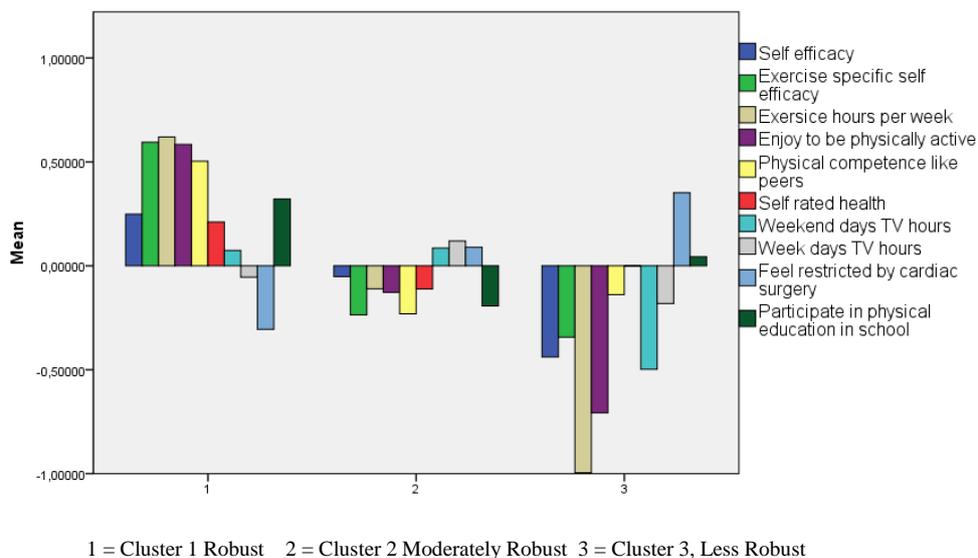
PE = physical education.

Self-rated health rated 1 – 4 , self-efficacy and exercise-specific self-efficacy 1 – 100, physical education at school, physical competence, enjoy physical activity, restricted by heart surgery rated 1 – 5; Hours active leisure time, Weekend and weekdays TV 0 – 7.

The significance value *p <.5 after Bonferroni correction between clusters after multivariate analyses of covariance.

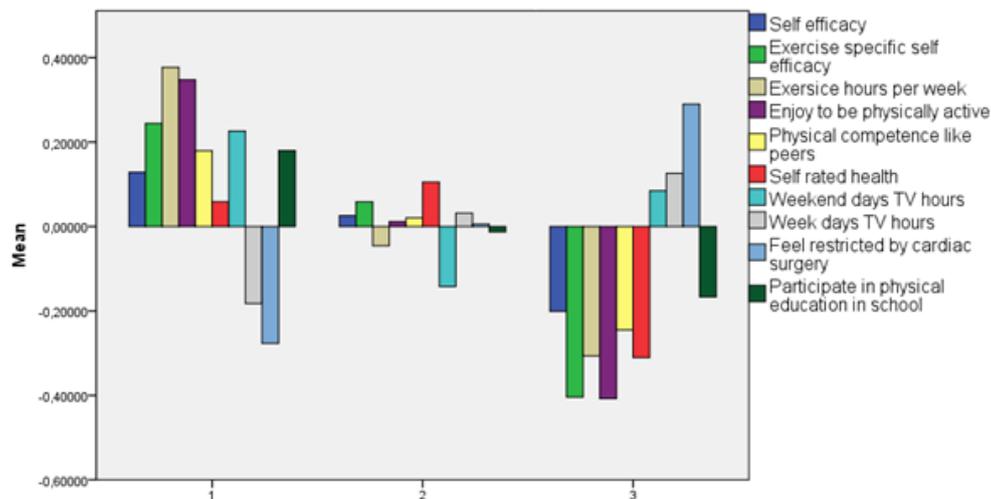
Girls in the *Robust* cluster lived a physically active lifestyle, according to their reported exercise-specific self-efficacy, exercise hours per week, enjoyment of physical activity and physical competence compared to peers. The opposite was the case with girls in the *Less robust* cluster, whose responses indicated a sedentary lifestyle.

Figure 7. Differences in lifestyle behaviors for adolescent girls across clusters, z-scores



Boys reported no differences in lifestyle behaviours between clusters, apart from differences in enjoyment of physical activity. Boys in the *Less robust* cluster enjoyed physical activity less than did the those in the *Robust* cluster, yet boys reported no differences across clusters in exercise-specific self-efficacy, exercise hours per week and physical competence compared with peers.

Figure 8. Differences in lifestyle behaviors for adolescent boys across clusters, z-scores



1 = Cluster 1 Robust 2 = Cluster 2 Moderately Robust 3 = Cluster 3, Less Robust

Conclusions of Study II

The cluster analysis attributed some of the variability in cardiorespiratory fitness among adolescents with CHD to lifestyle behaviours and physical confidence. Profiling health-related fitness offers a valuable new option in the management of person-centred health promotion. The cluster analysis revealed that some variability in health-related fitness among adolescents with CHD was unrelated to diagnoses. Girls and boys display dissimilar profiles, and more gender-specific research is needed to tailor health recommendations.

Discussion

The thesis contributes new knowledge about whether cardiac rehabilitation in adolescents with CHD can benefit from adding eHealth in the form of the Min.Puls.nu intervention to health education and individual counselling

Principal findings

This is the first randomized trial to test the effect of an eHealth intervention on maximal oxygen uptake, physical activity and health-related quality of life in adolescents with CHD. As the eHealth intervention was no better than the control intervention, we cannot recommend that the MinPuls.nu eHealth intervention designed for the trial, consisting of a 52-week Internet, mobile application, and SMS-based programme delivering individually tailored text messages to encourage physical activity, should be included in strategies for improving fitness in adolescents with complex CHD.

Health-related fitness profiling and its relationship to lifestyle behaviors offer a valuable new option in the management of person-centred health promotion among adolescents with complex CHD. Some of the variability in health-related fitness in adolescents with CHD can be attributed to lifestyle behaviours and enjoyment of physical activity, as opposed to diagnoses.

Limitations and strengths of the PReVaiL trial

Patients

Inclusion criteria

Rehabilitation studies in adolescents with CHD tend to investigate patients with Fontan-type circulation (60). However, patients with Fontan-type circulation are not representative of the total population of patients with CHD who need lifelong care. We included adolescents with no limitations in physical activity across diagnoses, which increased external validity. However, it also limits the generalizability to patients with limitations in physical activity. Being physically active on a regular basis may provide great benefits to all adolescents with CHD.

Although the PReVaiL trial is modest in size, it is larger than comparable trials. The level of interest in participating in the trial may reflect patient demand for cardiorespiratory exercise testing in this population as a part of regular assessments in Denmark. Including patients between the ages of 13 and 16 years could introduce confounding by great variations in growth spurt and maturity. However, stratification variables of gender and high/low peak oxygen uptake reduced differences in group composition. This is important because outcomes may be influenced by inadequately

balanced randomization due to lack of stratification for variables highly associated with the outcome (94). Selection bias may have been introduced because 18% of girls and 34% of boys were physically active for more than 60 minutes a day. A comparison with an age-matched Danish population found that the patients in PReVaiL were more physically active than were the age-matched peer group (76). However, data on the age-matched population were collected by survey, and results cannot be directly compared. Nonetheless, it is likely that the PReVaiL trial attracted adolescents with high motivation for physical activity.

To prevent selection bias at the level of parents, compensation for lost income (up to a modest limit) for the accompanying parent was an option. Selection bias may have been introduced in studies in which patients living far from specialist centres were enrolled as controls (41;68). Selection bias was avoided by randomizing patients nationwide. However, more test sites across the country may have led to the randomization of more patients. This potential limitation is balanced by the strengths of consistent data collection and uniform health education and individual coaching at a single test site.

Exclusion criteria

External validity may have been compromised by the exclusion of patients with genetic syndromes and mental retardation related to CHD, since genetic syndromes are present in 8-10% of patients with CHD (12). Excluding patients with genetic syndromes and disabilities from trials precludes the possibility of understanding how they may benefit from rehabilitation initiatives in the future.

No patients were excluded due to untreated asthma or a systolic blood pressure more than 150 mm Hg measured on the right arm on the day of testing. The initial exclusion criteria of forced expiratory volume in one second (FEV1) of less than 80% of expected proved to be too narrow and was disregarded after approval from the regional ethical committee.

Design

The PReVaiL trial was designed to lower the risk of bias using centralised computer-based randomization procedures, concealed allocation and blinding of assessors and statistician. The robust design increases confidence in the results (95).

The intervention drew on an existing and widely used eHealth platform that supported multiple eHealth applications (96). By adhering to the CONSORT criteria for eHealth interventions,

PReVaiL has the potential to inform future trials (56). A feasibility test assured that all procedures ran smoothly at the test site (71). Data collection procedures were tested and adjusted accordingly (97).

Adherence to the intervention was low (Figure 4). One potential explanation is that advances in newer technology led to low participant engagement in eHealth interventions to increase physical activity (98). The market for smart phone applications has markedly increased since we developed the intervention in 2009, and this application may have quickly become outdated. Expedient enrolment in trials testing eHealth interventions is important.

The process evaluation revealed that it was not possible to add activities to the mobile application retrospectively, which may have influenced adherence. In addition, unintended delivery of multiple daily SMS text messages may have decreased motivation or led to irritation. A more wide-ranging process evaluation before initiating the PReVaiL trial may have provided an opportunity to detect and address these undesirable features. Considering the amount of available funding in the Horizon 2020 programme directed toward using eHealth to empower citizens to manage their own health (59), researchers should carefully consider which eHealth trials may be worth conducting so as not to waste time and money. We suggest that future eHealth interventions should be thoroughly piloted and include a process evaluation by software developers to avoid problems of low adherence and high attrition in costly clinical trials.

Intervention

Ethics

Conducting research with minors involves careful ethical preparation and decisions to safeguard the ethical principles of autonomy, beneficence and justice (99). Autonomy, which refers to the ability to make a meaningful choice, was protected by supplying adequate verbal and written information to adolescents and parents and emphasizing the option of leaving the trial at any time with no consequences for future health care. Beneficence, referring to doing no harm as well as potential benefits that outweigh any risks, was supported by making certain that safety procedures were adhered to at all times. In addition, to monitor unintended negative consequences, registered health care contacts were assessed over time to determine if the intervention increased the number of health care consultations. Justice, which refers to fairness and appropriateness, was supported by

thorough literature reviews related to living with CHD among adolescents and parents in preparation for the trial.

Health education and individual coaching content adhered to recommendations for physical activity by the Danish National Board of Health, which are similar to international recommendations (100). We expected that many patients already knew of these recommendations. However, 14% of girls and 8% of boys did not participate in physical education at school on a regular basis (Table 6). Nonparticipation can be explained in several ways. It has been suggested that some adolescents may “play the congenital heart disease card”, based on the situational context (101). Parents and physical education teachers may find this challenging. Because school-based activities in general have a great potential to increase oxygen uptake in adolescents (102), future studies could address adherence to school-based interventions and public health guidelines and whether eHealth deserves a role in this scenario.

Bandura’s social cognitive theory targeting self-efficacy was applied to mediate sources for self-efficacy in relation to physical activity. (86) A guideline was developed to support this aim that addressed physical activity, diet, smoking, alcohol use and sleep. However, the degree of adherence to the guideline by the trial team was not assessed, which may limit external validity, although adherence to guidelines by the team is not expected to have influenced results.

Outcomes

Only 8 % of the patients were active users at the end of the intervention (Figure 4). This may influence the interpretation of the results, since the risk of a type II error—i.e. not finding a significant difference even though there is a difference—is probably high for detecting a difference in the development of VO₂ peak in the subgroup of patients who adhered to the protocol.

All tests were performed at the same site, using the same equipment operated by the same team. Inter-rater agreement was supported by a comprehensive orientation to all tests and a supplemental written guide to testing. Inter-rater reliability was not measured, however, and was a potential confounder.

A general strength of the trial was measuring the primary outcome both at baseline and after the intervention period. It was also a strength that the one-year intervention encompassed all four

seasons and that baseline and follow-up testing were conducted at the same time of the year, minimizing any bias from seasonal variations in VO₂ peak.

Primary outcome: peak oxygen uptake

The primary outcome, peak oxygen uptake, was assessed by a cardiopulmonary exercise test performed by a breath-by-breath gas analyser based on a maximal bike test to exhaustion, which increased the validity of the results compared to trials assessing outcomes by submaximal tests (73). The predetermined level for exhaustion of an RER of 1.1 was met, with a mean of 1.3 (SD 0.1) (Table A1) which increased internal validity. The protocol was designed to achieve exhaustion within 6 to 12 minutes which was achieved by 61% of participants, with a mean time to exhaustion of 8.3 minutes (SD 1.9).

Due to non-tolerance of the mask or equipment failure in five patients, max oxygen uptake was calculated based on the highest completed by the formula $VO_{2\max} \text{ (l/min)} = 0.16 + 0.011 (W_{\max})$. The possibility of introducing bias at outcome assessments may have been present because patients in the trial were not blinded to the intervention. Despite instructing patients to conceal their group assignment before final tests, we cannot guarantee that patients did so.

Secondary outcome: physical activity

Physical activity is a complex construct that can be classified quantitatively or qualitatively (34). Physical activity was assessed quantitatively by an accelerometer as well as qualitatively by validated questionnaire. Nevertheless, data should still be interpreted with caution. It was a strength that the accelerometer was set to measure at short intervals (5 seconds), since a short epoch interval better captures the burst movement patterns that characterize adolescence (103). New generation physical activity monitors, such as heart rate monitors (34), in combination with global position system (GPS) monitors (104), could have provided useful information regarding heart rate variability and movement patterns. The mobile application we used in this trial was already formatted to measure physical activity by an accelerometer; however, it did not seem appropriate to ask patients to use their mobile phones to monitor physical activity during sports and play.

Exploratory outcome: health-related quality of life

Health-related quality of life was evaluated by generic and disease-specific PedsQL, version 4.0. No overall effect of the intervention was found on health-related quality of life, and the domains were not analysed separately.

Feasibility testing of the questionnaire revealed that it was necessary to develop legends explaining the context of the PedsQI. Legends were consequently added to the page header of the web-based questionnaire and read aloud to all patients immediately before they responded. This may have strengthened the face validity of the questionnaire. However, it was a limitation that this was necessary for adolescents to understand how to respond to the questionnaire. The PedsQI was selected because of its use in several studies with healthy adolescents, as well as those with conditions such as diabetes and cancer (105-107), making comparisons possible. The disease-specific version of the PedsQI may not have been sensitive to this population because PReVaiL patients infrequently visited the hospital and used no medications.

The assessment of health-related quality of life could have been strengthened by choosing another tool after the feasibility test revealed face validity problems. A validated generic quality of life instrument for healthy adolescents used in Denmark, such as the KidsScreen, could have been used instead (108).

Statistics

All statistical analyses were conducted according to the published analysis plan (84). Multiple imputations were used to handle missing data (90), which allowed for intention-to-treat analyses. A trial in adults describing the use of intention-to-treat analyses excluded patients lost to follow up before the final analyses (109), which is a potentially highly biased approach because complete case analyses nearly always provide biased results (91). Patients lost to follow up may have had poorer outcomes than those attending the full intervention, which may partly explain why long term benefits were not observed.

The estimated effect size was based on the best available data at the start of the intervention. The minimal clinical relevant effect size is debatable because impaired ability to increase peak oxygen uptake is a part of the underlying condition. The mean effect size in a previous study was 2.8 ml/min/kg (61).

Limitations and strengths of the eHealth intervention

We were only able to randomize 158 patients out of the originally planned 216; of these, 50% completed the trial. Our sample size was estimated based on the standard deviation obtained from a watt max test in a small study with the highest methodological quality existing at the time the

protocol was written (71). Using the observed standard deviation of the present trial, based on the more precise outcome of VO_2 peak, the necessary sample size to detect a clinically relevant difference of $3.00 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}$ would be 160 patients. The 95% confidence interval for the primary outcome of this trial was -2.66 to 1.36, which excludes a clinically relevant effect. Consequently, it is unlikely that a larger sample size would have elicited a relevant effect (110).

Screen time spent behind personal computers, tablets or smart phones in adolescence is associated with unhealthy habits and lack of sleep (111). It may seem contradictory to use an eHealth intervention to increase physical activity in adolescents when screen time is associated with sedentary behaviour and maximal oxygen uptake in adolescents (112;113). However, the approach was intended to accommodate patients who were inactive at baseline and who would potentially opt out if activities became boring, too competitive or demanded too much time (114). The text messages were designed to encourage high intensity activities providing enjoyment and fun, not to add extra “homework”.

Limitations and strengths of the profiling of health relates fitness

The intention of the cluster analysis was to explore a novel understanding of fitness, physical activity and daily living in adolescents with CHD. Cluster analysis is a technique that has been used in exploratory studies and can be implemented in several ways. The selection of health-related fitness variables influenced the results of the cluster analysis, which is a main limitation of the technique (115). Another limitation is the necessary choice of clustering method and data handling before analyses are conducted (115). For instance, we did not transform the health-related fitness variables into z-scores before the clustering procedure, which meant that the largest numbers, in this case max load/kg, most heavily influenced the cluster allocation. However, the clusters were stable and the profiles seemed to make clinical sense.

The final outcome analyses were adjusted for cluster allocation but did not add any new information to the primary outcome. Subgroup analyses can falsely indicate that the treatment is beneficial in a particular subgroup when the trial shows no overall effect (116). Outcomes related to subgroups, such as gender, are not reported on a regular basis in this population. This may be due to small sample sizes leading to underpowered conclusions.

The cluster analysis yielded valuable information about the variability in this population. First, parents can be reassured that patterns of robustness extend beyond diagnosis and that robustness is associated with physical activity. Second, health care providers can be informed that it may be relevant to address sedentary behaviour as well as physical inactivity in adolescents with CHD. The finding that a subgroup of adolescent girls and boys are highly active may also need attention, since some adolescents with chronic illnesses are attracted to risk behaviours (117) .

Examining health-related fitness variables by cluster analysis adds information on physical fitness, which can be defined in terms of both performance and health (118). Performance-related fitness refers to components associated with optimal sports performance, such as peak oxygen uptake. Health-related physical fitness components refer to components associated with optimal health. Thus, a cluster analysis has potential advantages over more commonly used methods to identify characteristics of health in adolescents with CHD (119).

Comparison with other trials

Patient selection

Despite the fact that adolescence is considered a “window of opportunity” for health promotion not to be missed (120), only two other trials have investigated the effect of exercise training in adolescents with CHD (121;122). In the PReVaiL trial, the attrition rate was 25% over a 52-week intervention, and the adherence rate was only 56% despite a very low adherence threshold. This can partly be explained by the fact that several older patients changed schools while they were participating in the trial. Some even moved away from home to attend an “Efterskole” (boarding school). Among healthy adolescents, competing demands for time, such as homework and after-school jobs and social influences from friends, influence physical activity behaviours (123).

Morrison et.al. reported an attrition rate of 29.4% in a 26-week home-based intervention; adherence to the intervention was not reported (122). Dulfer et al. reported a median adherence to a facility-based exercise programme of 89% (interquartile range 79-100) in a 12-week intervention; attrition was 23%. In trials among adults, the attrition rate was 15% in a 10-week facility-based trial (109), and all patients in the intervention group were reported to be adherent. In a 24-week home-based trial the adherence was 67.7% (SD ± 20.5%) calculated as percentage of intended training time (124). Longmuir et al. undertook a 52-week trial in 61 children aged 5.9 to 11.7 years in which attrition was 7% (125). Since attrition is higher in adolescents than in adults, regardless of length of

intervention, adolescence may not be an ideal time for an intervention to increase physical activity. In contrast, childhood may be the window of opportunity that should not be missed.

However, social support has a substantial moderating effect that should not be overlooked. Parents play an important role in the choice of lifestyle behaviours in childhood and adolescence (126). In PReVaiL, all parents were indirectly involved by being active during the individual coaching before randomization. Social support by parents to patients in the intervention group was not sought directly, which may have influenced adherence to the eHealth intervention. It may have influenced the findings if parents and siblings or peers had been allowed to be active users of the mobile application along with the patient. However, it would also have influenced costs, as well as safety if peers had been invited to participate. Dulfer et al. found that parental mental health moderates the efficacy of exercise training on health-related quality of life (127). Parents whose children are born with CHD are expected to assume responsibility for their child's physical condition and must know how to act on physical deterioration (128). Parents may experience anxiety about physical activity, and to cope with adolescents' demands for more independence, it makes sense to introduce a rehabilitation intervention in childhood. Rehabilitation initiatives in older age groups may benefit from a solid foundation of motor skills and physical activity created in childhood.

Our intervention encouraged participants to increase their heart rate as often as possible for at least 10 minutes without monitoring their pulse. Pulse monitoring was part of interventions with adults during 10 to 12-week interventions (109;129). We decided against asking adolescents to monitor their pulse to gauge intensity of physical activities on a regular basis over 52 weeks, according to the ethical principle of justice. Moreover, the dose-response relationship between physical activity and health benefits is largely unknown in healthy adolescents (130), as well as in adolescents with CHD, and the ethical principle of beneficence could have been violated. Activity monitors that are discrete and can be worn for longer periods of time are in the development phase and may demonstrate usefulness in future research related to benefits and harms of physical activity.

Fewer girls than boys (42% vs. 68%) agreed to participate in the PReVaiL trial. This was also the case in trials including children, in which 42 % of the participants were girls (125), in two trials among adolescents in which 29% and 40% of participants were girls (122;131), and in a trial among adults, in which 35% of participants were women (124). The reasons that females from childhood

through adulthood are less likely to be included in trials that promote physical activity need consideration. Whether fewer girls are eligible or agree to participate is unknown, and qualitative research may help to both elucidate causal factors and point to effective ways to increase the participation of girls and women. In addition, gender-specific trials may be needed to adequately understand the relationship between physical activity and health benefits in girls and women.

In the PreVaiL trial, participants were stratified by gender to reduce risk of bias. Only one trial recruited the same number of men and women, but females (63%) were disproportionately allocated to the intervention group because assignment was not gender stratified (109). Bias may also have been introduced when more male patients were allocated to the intervention group (122). Given the evidence for gender-specific oxygen uptake in adolescents, it is suggested that oxygen uptake be analysed by gender in future research (132).

Design

We found a statistical non-significant increase in peak oxygen uptake in the control group receiving only health education and individual coaching that was not found in the group also receiving the eHealth encouragement. Although eHealth interventions may have a “gadget” appeal among adolescents, that appeal is apparently short lived. A trial with adolescents with diabetes type 1 that aimed to increase physical activity by text messaging in combination with the use of pedometers yielded similar results (133). Teixeira et.al found, based on a systematic review of 66 studies of what motivates individuals to exercise, support for a positive association between interventions that stimulate intrinsic motivation and long term exercise adherence (134). Intrinsic motivation is defined as doing an activity because of its inherent satisfaction, such as personal feelings of enjoyment and accomplishment. Extrinsic motivation refers to performing an activity to obtain outcomes separate from the activity itself, such as health outcomes. The SMS messages may have worked as extrinsic motivators and may have been regarded as a kind of “homework”, despite the intention of providing fun, rather than adding extra unwanted tasks for patients. In contrast, the health education and the individual counselling may have stimulated intrinsic motivation by validating and supporting the adolescents’ autonomy. This may in part explain why patients in the control group increased their peak oxygen uptake slightly over 52 weeks.

Enjoyment of physical activity was found to be a mediator of effects of a school-based physical activity intervention (135). Enjoyment of physical activity differed significantly between health-

related fitness profiles in the PReVaiL trial, indicating an important association. The direction of the association is unknown; however, enjoyment of physical activity is a central mediator for physical activity in children (136). A recent trial found that exercise training did not have an effect on sports enjoyment in adolescents with CHD (137), and the authors suggested that adolescents with CHD may see sports as being important for health benefits. The cluster analysis also found that enjoyment of physical activity and physical competence was associated with the robustness of health-related fitness. Lasting changes leading to increased physical activity in healthy adolescents seem to depend on intrinsic motivators, such as joy and physical activity for its own sake (138).

In a recent review of tele-rehabilitation for cardiac patients, the reviewers concluded that tele-rehabilitation appears to be feasible and effective, compared to conventional hospital rehabilitation, and that the next step is to take patient safety and health economics into account (139). It may be important to be more ambitious and take advantage of technological possibilities of making tele-rehabilitation person-centred even more successful than conventional rehabilitation.

Intervention

We tested a home-based eHealth intervention in which the software developer was responsible for all contact concerning the rehabilitation programme for 52 weeks. Our findings contrast with those of a recent home-based trial over 26 weeks in the same population (109). Patients were contacted by the research team by telephone once a month to check on their progress with their exercise plan, and patients could contact the research team at any point, making the interventions hard to compare. Regular contact once a month is not unusual in trials to obtain feedback (125) or to check on progress with the exercise plan (122). Similarly, home-based trials may email asking about progress once a week, followed by a telephone call in the case of no reply (109). Regular personal contact may be associated with increased short-term effectiveness of interventions, as well as increased costs, although sustainability is in question.

Outcomes

Peak oxygen uptake was chosen as the primary outcome because it is a predictor for mortality and morbidity in adults with CHD (63). This predictive effect may be confounded because the data were generated from more symptomatic patients treated at a tertiary specialist centre (140). Peak oxygen uptake is a surrogate outcome and should be interpreted with caution because surrogate outcomes do not always have an effect on clinically meaningful outcomes, such as mortality and morbidity

(141;142). However, peak oxygen uptake is acknowledged as a robust outcome in heart disease (143). No trials have reported effects at one year or later on peak oxygen uptake in this patient group (144). It is questionable which outcome of rehabilitation trials in adolescents with CHD is the most relevant.

One previous trial showed that aerobic exercise in patients aged 10 to 15 had a significant effect on health-related quality of life after 12 weeks of training; however, no effect was found in patients aged 16 to 25 (131). Numerous health-related quality of life instruments are available, and there is no consensus on the definition of the concept, nor which instrument to use (145). Furthermore, there is no consensus on whether patients with CHD score higher or lower than their healthy peers.(146)

Diverse outcomes have been assessed in recent trials with adolescents with CHD, ranging from effect on the cardiac muscle (129) to sports enjoyment and emotional problems (121;137). Sedentary behaviour has not been addressed specifically but could prove to be an effective outcome in trials addressing adolescents (147). In the cluster analysis, we found significant between-cluster differences in hand grip strength, indicating that muscle strength is associated with overall robustness (Table 4, Table 5). Recent research indicates that young adults with CHD have generalised muscle weakness (24;148). Since motor development is impaired in some children with CHD, it may be of value to explore muscle strength further in childhood and adolescence (25;149) and ensure relevant rehabilitation as needed. One small study found that isolated muscle training without additional aerobic training improved muscle mass as well as cardiac function and exercise capacity in adults with Fontan-type circulation (150). Muscular fitness is an important component of overall health-related fitness, as well as a predictor of current and future health in adolescents (151). Strength training in patients with CHD is traditionally discouraged due to pressure overload that can be difficult to control (46), but it may be considered in future trials.

In this trial, patients in the control group were counselled to independently select and plan specific types of physical activity. Self-determination may partially account for the slight increase in the point estimate of peak oxygen uptake in the control group (134;152). However, behavioural change strategies are rarely used in trials to promote physical activity in adolescents with CHD, and more evidence is needed.

It is somewhat surprising that the majority of research has focused on how much individuals can be held responsible for their behaviour. Physical activity is a complex entity and the potential mechanisms of change are multifactorial. Evidence-based lessons from around the world emphasise that interventions to promote physical activity have increased effectiveness when public health strategies support individual initiatives by ensuring safe biking lanes and making healthy living an option for most people (149).

Genetics play a major role in trainability (153). In addition to an unknown dose-response relationship between physical activity and health outcomes, research on physical activity in the future may be based on cultural as well as genetic mapping and Mendelian randomization (154).

Conclusions

Based on the findings in this thesis, the following conclusions can be drawn from the PReVaiL trial:

- The eHealth intervention was no better than the control intervention. Therefore, we cannot recommend including our designed MinPuls.nu eHealth intervention, consisting of a 52-week Internet, mobile application, and SMS-based programme delivering individually tailored text messages to encourage physical activity, in strategies for improving fitness in adolescents with complex CHD.
- Health-related fitness profiling and its relationship to lifestyle behaviors offers a valuable new option in the management of person-centred health promotion among adolescents with complex CHD. Some of the variability in health-related fitness in adolescents with CHD can be attributed to lifestyle behaviours and enjoyment of physical activity, as opposed to diagnoses.

Recommendations for clinical practice

In the light of an increasing interest in promoting physical activities in school settings, future interventions could aim at preparing adolescents with CHD to enjoy physical activity with peers at school. Adolescents in the PReVaiL trial reported no differences in participation in physical education classes at school, yet their participation was not reflected in health-related fitness profiles. Tailored and person-centred interventions are needed. Interventions should take place that cover the entire lifespan and could start with parents in early childhood, as suggested by Longmuir et al. (125). Addressing fundamental developmental movement and motor skills, such as balance, from an early age and strengthening social support from parents may be important moderators of physical activity enjoyment in patients with CHD. The paediatric rationale that participation in physical activities and sports adds to the enjoyment of life may be a leading thread to follow.

A central objective of all previous interventions has been to increase physical activity (60;61). Given the low success rates of these programs, investigators could consider re-examining the design of youth interventions. In healthy adolescents, longitudinal programs that focus on stemming the age-related decline in physical activity have been effective (132). The association between robustness and sedentary behaviours we found in the cluster analysis suggests it is likely that this kind of program may also be highly relevant for patients with CHD. Future trials are needed to test this hypothesis.

Perspectives and future research

- Incorporating IT software with “growing pains” into care may not only waste time and money, it may also hamper patients’ confidence in health care. Software should be thoroughly tested by the IT industry before being introduced to patients in trials. Future research may clarify ways to ease communication to support adjustments to better align with patients’ needs and wishes. Communication with the IT industry is demanding because of many technological aspects unknown to health care providers. Finding the right solutions for the right patients at an appropriate cost-benefit ratio is an ever-changing task.
- Future research could explore if eHealth rehabilitation initiatives can be “turned off and turned on” to accommodate competing demands in people’s lives. Text messages to patients compete with many other tasks during daily living. Health status also changes, as do the

resources individuals can devote to promoting and sustaining healthy habits. Some patients may need a higher degree of personal contact and may not benefit from an eHealth initiative alone. Isolation may become a potential problem for patients needing care for several health problems. It is important to know who these patients are to ensure appropriate treatment and care for all.

Summaries

English summary

Background

Congenital heart disease is the most frequent congenital disorder and the most frequent cause of infant death from birth defects. Today, more than 85% of all patients are expected to live to adulthood. While exercise capacity is an important predictor of survival, the level of physical activity and exercise capacity in adolescents with complex congenital heart disease has been reported to be significantly impaired. Consequently, physical activity in adolescents should be encouraged to protect them from comorbidities.

eHealth - health care delivered or supported through the Internet and related technologies - has the potential to eliminate distance barriers for physical activity coaching, and provide access to medical services that would not be available in distant communities.

The primary aim of this thesis was to assess the effect of adding a home-based eHealth intervention to health education and individual counselling for adolescents with congenital heart disease.

The secondary aim was to identify clusters of adolescents with congenital heart disease and examine lifestyle behaviour differences between clusters.

Methods

We conducted a clinical trial, in which we randomly assigned adolescents, 13-16 years with congenital heart disease, assigned to life-long medical follow-up, to eHealth encouragement physical activity for 52 weeks. All participants received a control intervention consisting of 45 minutes of group-based health education and 15 minutes of individual counselling involving patients' parents. The primary outcome was maximal oxygen uptake (VO_2 peak) after 52 weeks.

Using baseline data, a cluster analysis was conducted to identify profiles with similar health-related fitness. For comparisons between clusters, MANOVA analyses were used to test the differences in lifestyle behaviours.

Results

In the primary analysis, there was no statistically significant difference between intervention and control at follow-up. Adjusted for baseline values, the difference between the intervention group and the control group in mean VO_2 peak after 52 weeks was $-0.65 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (95% CI -2.66 to 1.36).

Three distinct profiles of health-related fitness were formed by the cluster analysis: 1) *Robust* (n=43, 27%); 2) *Moderately Robust* (n=85, 54%); and 3) *Less robust* (n=30, 19%). The participants in the *Robust* clusters reported leading a physically active lifestyle and participants in the *Less robust* cluster reported leading a sedentary lifestyle.

Conclusion

The eHealth intervention was no better than the control intervention. We cannot recommend that our designed MinPuls.nu eHealth intervention to be included in strategies for improving fitness in adolescents with complex congenital heart disease.

Further we conclude that health-related fitness profiling and its relationship to lifestyle behaviors offer a valuable new option in the management of person-centred health promotion among adolescents with complex congenital heart disease.

Dansk resumé

Baggrund

Medfødt hjertesygdom er den hyppigste medfødte misdannelse, og den hyppigste årsag til spædbarnsdød på grund af medfødte misdannelser. I dag forventes det at 85 % af alle patienter overlever til voksenalderen. Fysisk kapacitet er en vigtig prædiktor for overlevelse. Flere studier har fundet at unge med medfødt hjertesygdom har nedsat fysisk aktivitet og fysisk kapacitet. For at nedsætte risikoen for tilstødende livsstilssygdomme, bør unge med medfødt hjertesygdom opfordres til at være fysisk aktive

eHealth – her forstået som sundhedsydelser der understøttes elektronisk af Internettet og relaterede teknologier – har potentialet til at overkomme fysiske barrierer, og på den måde være med til at tilbyde bedre adgang til sundhedsydelser der ellers ikke ville være tilgængelige i yderområder.

Afhandlingens formål var primært at vurdere effekten af at tilføje en hjemme-baseret eHealth intervention til en sundhedssamtale samt individuel rådgivning til unge med en medfødt hjertesygdom.

Det sekundære formål var at identificere subgrupper af de unge i forhold til deres fysiske form, og at undersøge om der var forskelle på livsstilen mellem grupperne.

Metode

Vi gennemførte en undersøgelse hvor unge på 13 – 16 år med medfødt hjertesygdom, henvist til livslang opfølgning, blev randomiseret til eHealth med opfordring til fysisk aktivitet gennem 52 uger. Alle deltagerne gennemførte en kontrol intervention bestående af en 45 minutters gruppebaseret sundhedssamtale, samt 15 minutters individuel rådgivning sammen med deres forældre. Det primære effektmål var maksimalt iltoptag/kondital (VO_2 peak) efter 52 uger.

Vi foretog en cluster analyse på baggrund af baseline data for at identificere subgrupper med samme fysiske form, og sammenlignede subgruppernes livsstil.

Resultat

For det primære effektmål var der ikke statistisk signifikant forskel mellem grupperne ved opfølgningen. Vi fandt at forskellen i maksimalt iltoptag/kondital (VO_2 peak), justeret for baseline værdier, mellem interventionsgruppen og kontrolgruppen efter 52 uger, var $-0.65 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (95% CI -2.66 to 1.36).

Vi fandt at der var tre subgrupper der adskilte sig fra hinanden i forhold til fysisk form. 1) en *Robust* (n=43,27 %); 2) en *Moderat Robust* (n=85,54 %); og 3) en *Mindre Robust* (n=30,19 %). Deltagerne der tilhørte den Robuste subgruppe havde en fysisk aktiv livsstil, og deltagerne der tilhørte den Mindre robuste gruppe havde en inaktiv livsstil.

Konklusion

eHealth interventionen var ikke bedre end kontrol interventionen. Vi kan derfor ikke anbefale, at den eHealth intervention, som vi udviklede, bliver inkluderet i strategier til at fremme fysisk kapacitet blandt unge med medfødt hjertesygdom.

Samtidig konkluderer vi, at subgruppe analyser i forhold til fysisk form, samt disse subgruppers relation til livsstil, kan bidrage til varettagelse af person centreret sundhedsfremme blandt unge med en medfødt hjertesygdom.

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Appendix A

Table A1. Baseline characteristics of participants

	Intervention group n = 81	Control group n = 77	P values
Age in years, mean (SD)	14.6 (1.3)	14.6 (1.2)	0.764
Baseline anthropometrics, mean (SD)			
Height, cm	166 (10.4)	165 (9.5)	0.553
Weight, kg	57.0 (11.0)	58.0 (13.4)	0.704
BMI	20.0 (2.9)	20.5 (3.9)	0.377
Body surface area m ²	1.6 (0.2)	1.6 (0.2)	0.918
Waist, cm	72.0 (7.9)	73.0 (9.1)	0.422
Hip, cm	87.7 (8.6)	88.4 (10.6)	0.678
Waist/hip ratio	0.82 (0.07)	0.83 (0.07)	0.530
Sum of skinfolds 4 sites, mm	13.3 (8.5)	12.5 (8.2)	0.579
Systolic blood pressure, mm HG	119 (12.7)	118 (10.8)	0.456
Diastolic blood pressure, mm HG	67.1 (6.6)	67 (6.7)	0.736
Resting pulse, beats per minute	69.2 (11.4)	71 (9.9)	0.303
Muscle strength,	29.1 (8.5)	27.9 (7.5)	0.232
Baseline lung function, mean (SD)			
FEV1	3.0 (0.7)	3.0 (0.7)	0.954
FEV 1 % of predicted	94 (0.1)	94 (0.1)	0.816
FVC	3.1 (0.8)	3.5 (0.7)	0.655
FVC % of predicted	90 (0.1)	90 (0.1)	0.988
PEF l/min	364 (77.8)	356 (105.8)	0.584
FEV1/FVC	86.3 (7.9)	86.6 (7.4)	0.782
Cardiorespiratory fitness, mean (SD)			
Peak oxygen uptake, ml/min/kg	43.7 (9.8)	43.4 (9.3)	0.820
HRR, beats per minute	122.8 (15.1)	122.0 (15.9)	0.782
Oxygen pulse	13.1 (3.3)	12.9 (3.6)	0.813
Max work load, watts	185 (48.1)	182 (46.6)	0.671
Anaerobic threshold, VO ₂ /kg/min	0.7 (0.2)	0.7 (0.1)	0.534
RER	1.3(0.1)	1.3 (0.1)	0.580
Physical activity			
Time physical activity, minutes, mean (SD)	438 (159)	475 (176)	0.173
MVPA ≥ 60 minutes a day, %	32	26	0.473
Minutes ≥ 2000 counts, mean (SD)	45.8 (24.1)	49.8 (26.6)	0.331

Leisure time, hours per week day, mean (SD)	3.1 (.7)	2.9 (.2)	0.413
Sedentary time. hours per week day, mean (SD)	3.2 (1.6)	3.2 (1.7)	0.890
Sedentary time. hours per weekend day, mean (SD)	4.9 (1.9)	4.4 (1.9)	0.094
Physical activity, number (%)			
Bike to school most days	39 (50)	46 (57)	0.270
More physical competent than peers	21 (26)	23 (30)	0.729
Enjoy physical activity	68 (84)	60 (78)	0.223
Participate physical education at school most times	75 (83)	67 (87)	0.185
Physical active during breaks	8 (10)	11 (14)	0.356
Health-related quality of life			
Generic HRQoL, mean (SD)	80.00 (9.4)	80.43 (9.5)	0.755
Disease-specific HRQoL, mean (SD)	85.21 (10.7)	84.59 (9.7)	0.807

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume at one second; FVC, forced vital capacity; HRQoL, health-related quality of life; HRR, heart rate reserve; MVPA, moderate to vigorous physical activity; PEF, peak expiratory flow; RER, respiratory exchange ratio

Papers I – III

Paper I

Klausen SH, Mikkelsen UR, Hirth A, Wetterslev J, Kjaergaard H, Sondergaard L, et al. Design and rationale for the PREVAIL study: effect of e-Health individually tailored encouragements to physical exercise on aerobic fitness among adolescents with congenital heart disease--a randomized clinical trial. *Am Heart J* 2012 Apr;163(4):549-56.

Design and rationale for the PREVAIL study: Effect of e-Health individually tailored encouragements to physical exercise on aerobic fitness among adolescents with congenital heart disease—a randomized clinical trial

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Intensive exercise may be an important part of rehabilitation in patients with congenital heart disease (CHD). However, performing regular physical exercise is challenging for many adolescent patients. Consequently, effective exercise encouragements may be needed. Little is known on the effect of e-Health encouragements on physical fitness, physical activity, and health-related quality of life in adolescents.

This trial is a nationwide interactive e-Health rehabilitation study lasting 1 year, centered on interactive use of mobile phone and Internet technology. We hypothesize that e-Health encouragements and interactive monitoring of intensive exercise for 1 year can improve physical fitness, physical activity, and health-related quality of life.

Two hundred sixteen adolescents (age, 13-16 years) with surgically corrected complex CHD but without significant hemodynamic residual defects and no restrictions to participate in physical activity are in the process of being enrolled by invitation after informed consent.

Physical fitness is measured as the maximal oxygen uptake ($\dot{V}O_2$) at baseline and after 12 months by an assessor blinded to the randomization group. After baseline testing, the patients are 1:1 randomized to an intervention group or a control group.

Individually fully automated tailored e-Health encouragements—SMS, Internet, and mobile applications—aimed at increasing physical activity are delivered to the participants in the intervention group once a week. The Bandura's Social Cognitive Theory inspires the behavioral theoretical background. The e-Health intervention and the Godfrey cycle ergometer protocol have been feasibility tested and seem applicable to adolescents with CHD. The trial is expected to contribute with new knowledge regarding how physical activity in adolescents with CHD can be increased and, possibly, comorbidity be reduced. (Am Heart J 2012;163:549-56.)

Background

The impact of cardiovascular disease is of great concern worldwide because 0.5% to 2% of the adult population is

affected. The burden of disability is substantial, and the prognosis may be poor.¹ This goes along with adding a significant economical burden to the health care system.

Over the last 20 years, there has been a growing population of adults with congenital heart disease (CHD).² The prognosis for morbidity and mortality for this group is unknown because only a minority of the patients have reached the age of 50 years.³ Congenital heart disease is the most frequent subgroup of congenital malformations with a prevalence of 7.9 of 1000 live births in Denmark.⁴ Within the next decade, 25 000 people in Denmark will live with CHD.⁴ Despite improved outcome in terms of survival, systemic hypertension and atherosclerotic disease add to the increased risk for heart failure and compound their problems.⁵ Together with ongoing medical problems, the patients experience feelings of being different, which has an impact on the patients health-related quality of life on a daily basis.⁶

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The overall aim of treatment and care for children with CHD is to provide them with the opportunity to live as normally and satisfactory as possible, compared with their healthy peers.⁷ Among the general population, higher levels of physical activity are associated with better mental health and reduced risk of obesity and other metabolic and cardiovascular diseases.⁸

A systematic review of the existing evidence base was undertaken by searching the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and Science Citation Index Expanded until January 2, 2010. This review revealed 23 studies and no reports of randomized clinical trials testing the hypothesis that long-term encouragements to exercise can improve physical fitness in patients with CHD. Protocols and outcome measures for exercise testing and training of patients with CHD were scrutinized for development of the study.

The level of physical activity and fitness in adolescents with complex CHD compared with healthy children is significantly impaired.^{9,10} This is probably lifestyle related because patients with CHD have the similar potential to improve their physical fitness by physical activity as their healthy peers.¹¹ Performing regular physical exercise is challenging for children and adolescents with CHD, and encouragements to an active lifestyle are needed.¹²⁻¹⁴

To develop a lifestyle behavior intervention to improve physical activity and physical fitness, exercise training programs in children and adolescents with CHD have been tested since 1981.¹⁵ Selection bias has compromised the results of the studies, and only a few interventions had an impact on VO_2 -peak.¹⁶ None of the studies focused specifically on the change of long-term health behavior, and no studies had self-efficacy in relation to physical activity as an issue. The optimal study and design of pediatric rehabilitation programs does not exist.¹⁶ Further investigations are needed to elucidate the most effective rehabilitation strategies for adolescents with CHD.

Mobile phones and Internet-based programs are increasingly used in self-management interventions and are potential tools for enhancing physical activity among adolescents with CHD. Significant changes in physical activity have been demonstrated in a similar randomized trial with e-mail support including 124 healthy adolescents with a mean age of 14.1 ± 0.8 years.¹⁷ A systematic review of technology-based interventions for promoting changes in physical activity in children and adolescents found that 7 of 9 studies indicated positive and significant changes in at least 1 psychosocial or behavioral physical activity outcome.¹⁸ The use of a behavior change theory was associated with enhanced intervention efficacy.¹⁸

This trial introduces an e-Health rehabilitation program lasting 1 year, centered on the interactive use of mobile phone and Web-based technology. Bandura's Social

Table 1. Feasibility test baseline data

	Minimum	Maximum	Mean \pm 1 SD
Age (y)	12.7	14.2	13.5 \pm 0.6
Height (cm)	153.5	176.0	162.8 \pm 7.8
Weight (kg)	47.0	55.7	50.7 \pm 3.2
BMI (kg/m^2)	17.6	20.0	19.1 \pm 1.0
VO_2 (mL/min)	2000.0	2855.0	2469.3 \pm 345.7
VCO_2 (mL/min)	2087.0	3161.0	2717.0 \pm 423.6
VO_2 ($\text{mL kg}^{-1} \text{min}^{-1}$)	41.2	55.4	48.8 \pm 5.2
RER	1.1	1.2	1.2 \pm 0.0
AT (mL/min)	0.6	0.7	0.7 \pm 0.1
Load (W)	150.0	225.0	179.2 \pm 29.2
HR (beats/min)	182.0	196.0	188.8 \pm 5.1
FEV ₁ (% predicted)	85	97	91 \pm 5.2
FEV ₁ (L)	2,4	3,4	2,8 \pm 0,4

BMI indicates Body mass index; VCO_2 , carbon dioxide production; RER, respiratory exchange ratio; AT, anaerobic threshold; HR, heart rate; FEV₁, forced expiratory volume in 1 second.

Cognitive Theory, including the concept of self-efficacy, guided the development of the intervention.¹⁹

We hypothesize that mobile phone and Web-based encouragements to increase physical activity, as well as interactive monitoring of physical activity for 1 year, can improve physical fitness, physical activity, and quality of life.

Trial design

The trial is a randomized clinical trial. Eligible participants are randomized in a 1:1 allocation ratio to 1 of 2 arms: an intervention arm, in which the participants receive individually tailored encouragements to increase physical activity via their mobile phones in addition to the control intervention defined below, and a control arm, in which they receive the control intervention only. The trial conforms to the CONSORT criteria for research on e-Health interventions recommended by Baker et al.²⁰

The e-Health program has been feasibility tested. Sign-on procedures and Web site was adapted according to evaluation. One healthy adolescent and 6 adolescents with CHD tested the feasibility of the exercise test protocol and repeated the test after 6 weeks. The participants with CHD could, without any problems, complete the baseline tests with excellent reproducibility: intraclass correlation coefficient 0.99 (Table 1, feasibility test baseline data).

Participants

The patients with CHD included in this trial are adolescents with repaired heart lesions in need of lifelong medical follow-up. Patients 13 to 16 years of age from the University Hospitals in Skejby and Rigshospitalet in Denmark with repaired complex CHD, truncus arteriosus communis, transposition of the great arteries,

double-outlet right ventricle (including Taussig-Bing anomaly), congenital corrected transposition of the great arteries, atrioventricular septal defect, tetralogy of Fallot, Ebstein anomaly, subvalvular aortic stenosis, supravalvular aortic stenosis, and coarctation of aorta without clinically important residual defect are in the process of being enrolled by invitation. All patients are permitted to participate in competitive sports and have no restrictions to physical activity.

Patients are excluded if they have been diagnosed as having a syndrome or a developmental disability, experience arrhythmia or have a device implanted (pacemaker, biventricular pacemaker, or intracardiac defibrillator), and have clinical signs of heart failure or other major illnesses. Furthermore, forced expiratory volume in 1 second <80% of expected, or systolic blood pressure >150 mm Hg measured on the right arm at the day of testing, leads to exclusion.

Interventions

Participants in the control and experimental groups receive 1 hour of health education before randomization. In addition, the experimental group receives e-Health encouragements throughout the 1-year interventional period.

Control intervention

All patients in the trial will receive health education. This includes 1 group counseling session before baseline testing, mainly focusing on physical activity and, to a less extent, also dealing with smoking, alcohol, diet, and sleep. A session lasts 1 hour and comprises 3 to 5 peers of the same sex. Goal setting, peer teaching, and problem-solving support are the techniques applied. The pedagogical framework for health education is inspired by Bandura's social cognitive approach for promotion of self-efficacy.¹⁹ Self-efficacy, rather than severity of the disease, is the most influential factor in determining whether adolescents will engage in sports or other physical activities.²¹

Experimental intervention

A 52-week Internet, mobile application, and SMS-based program provides individually tailored encouragements to physical exercise. To individually tailor the intervention in relation to physical capacity, the following question is asked when signing up for the e-Health program: how do you assess your fitness? The question is to be answered on a 5-point Likert scale from "Very Good" to "Very Poor." According to the reply, challenges are posed on beginner's level, middle level, or experienced level. The goal of the program is to have individuals participate in intense physical exercise in line with the current recommendations for healthy adolescents.²²

The participants are approached by a new challenge every week: for example, "The challenge this week is that you must run the longest trip you've ever run. Try to see how long you can keep yourself going." The participants add the number of minutes and type of exercise to a mobile application and register the results on a personal home page (<http://www.minpuls.nu/>). Educational materials and tracking and simulation tools are available. The participant only has access to the personalized Web page. The program consists of 3 main approaches: health education, tailored interactive text encouragements, and a personal exercise-planning tool.

The choice of the components is sought to adhere to adolescents' lifestyle preferences concerning individuality, control, and competition.²³

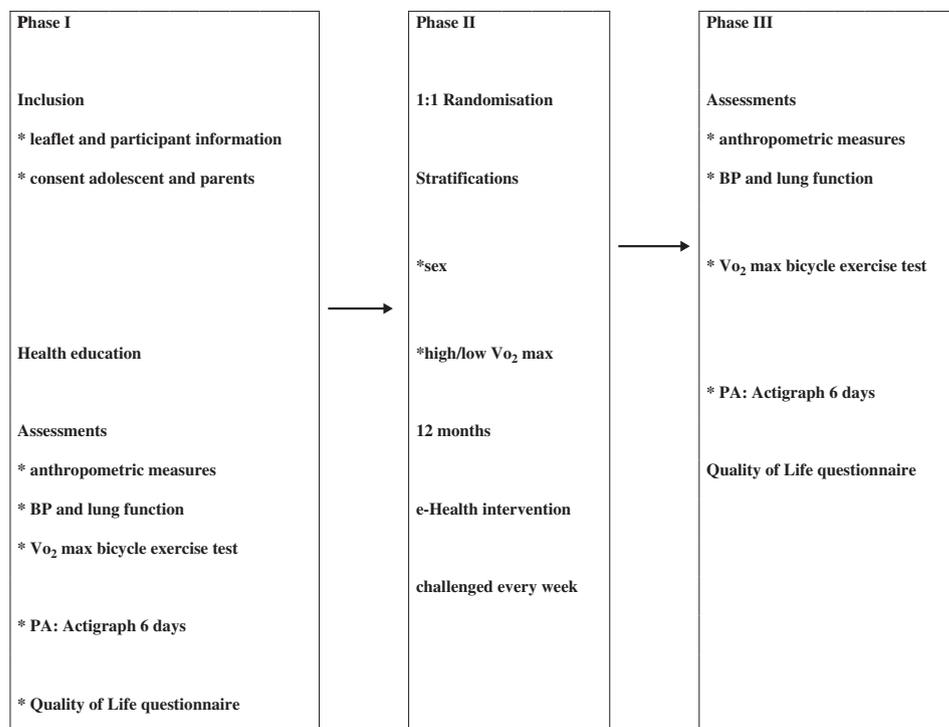
A private software deliverer (Mobile Fitness, Copenhagen, Denmark) is responsible for the portal and has developed the software tool called *MinPuls.nu*, in collaboration with the coordinating investigator and a group of stakeholders: a patient focus group and an expert panel comprising specialized nurses in cardiac adolescent medicine, specialist physiotherapist in pediatric cardiology, and specialists in exercise physiology. The title *MinPuls.nu* refers to *Me*, I am an adolescent—my *Pulse* must come up, so I can experience well being *now* (*MyPulse.now*).

When assigned to the intervention group, the patient's and the parent's telephone numbers and e-mail addresses, as well as the patient's trial registration number, are given to the software developer. The software developer is thereafter responsible for the communications concerning the rehabilitation program with the patients and their parents during the following year (Figure 1, study phases).

Primary outcome

The primary outcome is aerobic fitness measured via VO_2 -peak with a 12-month interval. Peak VO_2 has been found to be an independent predictor of death and/or hospitalization in patients with complex CHD.^{24,25} Aerobic fitness is assessed as the maximal VO_2 rate normalized to bodyweight (VO_2 -peak) during an incremental load test using an electronically braked ergometer cycle (Monark 839 Ergomedic, Proterapi, Brøndby, Denmark). Oxygen uptake, carbon dioxide elimination, and ventilation volume per time are measured with a computerized breath-by-breath analyzer (Master Screen CPX; Care Fusion, San Diego, CA).

After a 10-minute warm-up, the patient undergoes the Godfrey cycle ergometer protocol to elicit a maximal VO_2 response. With the aim to complete the test within 8 to 12 minutes, the boys are starting at 25 W and increase 25 W every minute, and the girls start at 20 W and increase 20 W every minute as described by Takken et al.²⁶ The criterion for ending the test is patient exhaustion or if the patient develops exercise-induced

Figure 1

Study phases. BP indicates blood pressure; VO_2 max, maximal VO_2 ; PA, physical activity.

physiological signs or complaints that warrant a termination of the test. Clinical criteria for terminating the test are as follows²⁶:

- Symptoms: chest pain, severe headache, dizziness, chills, sustained nausea, or inappropriate dyspnea.
- Signs: sustained pallor, clammy skin, disorientation, or inappropriate affect.
- Patient's requests for termination of the test.

The tests takes place in a well-ventilated exercise laboratory $>23 \text{ m}^2$ at the Institute of Sports Medicine at University Hospital Bispebjerg in Copenhagen by an experienced exercise physiologist skilled in interpretation of exercise tests.²⁶ Achievement of maximal VO_2 is evaluated by the following criteria: a respiratory exchange ratio of ≥ 1.1 to 1.2 and heart rate near maximum. Furthermore, attainment of a plateau in VO_2 despite an increase in workload is desirable.

Secondary outcome

The secondary outcome is physical activity. Physical activity is assessed using the GTIM Accelerometer (Actigraph model 77146, Pensacola, FL), which measures

the vertical acceleration of the body movement. Physical activity is monitored for 6 consecutive days immediately after the baseline tests and immediately before the outcome test: 2 weekend days and 4 weekdays. The criteria for a successful recording are a minimum of 3 days of 10 hours recording per day. Days with more than 10 hours of recordings but with periods where the accelerometer is not worn will be adjusted to a full day of 14 hours (estimated awake time for this population).⁸ The participants are asked to carry the accelerometer on the left hip from the morning until going to bed, beginning the day after the baseline testing as well as 6 consecutive days after the final testing. Data will be compared with comparator cases from studies using an identical protocol. A post-stamped return envelope and written and verbal instructions are given to the child and their parents. The Actigraph is a reliable and valid tool to measure activity in adolescents.⁸ The main derived physical activity parameter is the mean accelerometer counts per minute over the period of measurement.

The adolescents' self-rated physical activity is assessed by questions related to time, frequency, and intensity of physical activity as well as sedentary activities. Furthermore, self-efficacy related to exercise is analyzed.

Tertiary outcome

The tertiary outcome is health-related quality of life. Health-related quality of life is investigated using the Danish version of the Paediatric Quality of Life Inventory (Mapi, Lyon, France) for teens (ages 13-18 years), a generic module that assesses 4 domains of quality of life (physical functioning, emotional functioning, social functioning, and school functioning). The disease-specific module, which assesses 6 domains of quality of life (heart problems and treatment, treatment II, perceived physical appearance, treatment anxiety, cognitive problems, and communication), was translated and linguistically validated by 6 age-matched patients and 12 healthy adolescents according to guidelines.²⁷

Adherence to the program is assessed by numbers of log-ins and use of applications (time, type, frequency, and intensity of registered physical activities). System failures and changes made to the Web site are accounted for. Type of assistance offered to sign-up procedure is recorded.

Anthropometric data

Height is measured without shoes to the nearest 0.5 cm. Weight is measured in light clothing to the nearest 0.1 kg using Tanita Fat Weight Scale BF-300 GS (Frederiksberg Vægtfabrik, Frederiksberg C, Denmark). Body mass index is calculated and evaluated as of Danish reference values.²² Waist circumference is measured midway between the lower rib margin and the iliac crest with a nonflexible tape. Hip circumference is measured as the maximum circumference over the buttocks, with the measuring tape in a horizontal line. Body surface area is calculated ad modum Mostellar: body surface area (m^2) = (height [cm] × weight [kg]/3600). Skinfold thickness is measured with Harpenden Skinfold Caliper (Proterapi, Brøndby, Denmark) at 4 sites: the biceps, triceps, subscapular, and suprailiac sites. Calculation of body fat percentage from skin folds is performed according to Slaughter et al.²⁸ Blood pressure is measured on the right arm using Med Microlife BP A100 Plus (Microlife AG 9443, Widnau, Switzerland). A North Coast Hydraulic Dynamometer (Procare, Roskilde, Denmark) measures hand-grip strength, and the highest of 3 values is recorded.²⁹ Before exertion, a spirometric measurement is performed to assess the patients' forced vital capacity and forced expired volume in 1 second according to guidelines by SpiroUSB (Intramedic, Gentofte, Denmark). Standard equations (European Community for Coal and Steel) were used to generate the predicted values for the baseline spirometric parameters.³⁰

Sample size calculation

Sample size is determined and guided by previous research with adolescents with CHD. Assuming that the

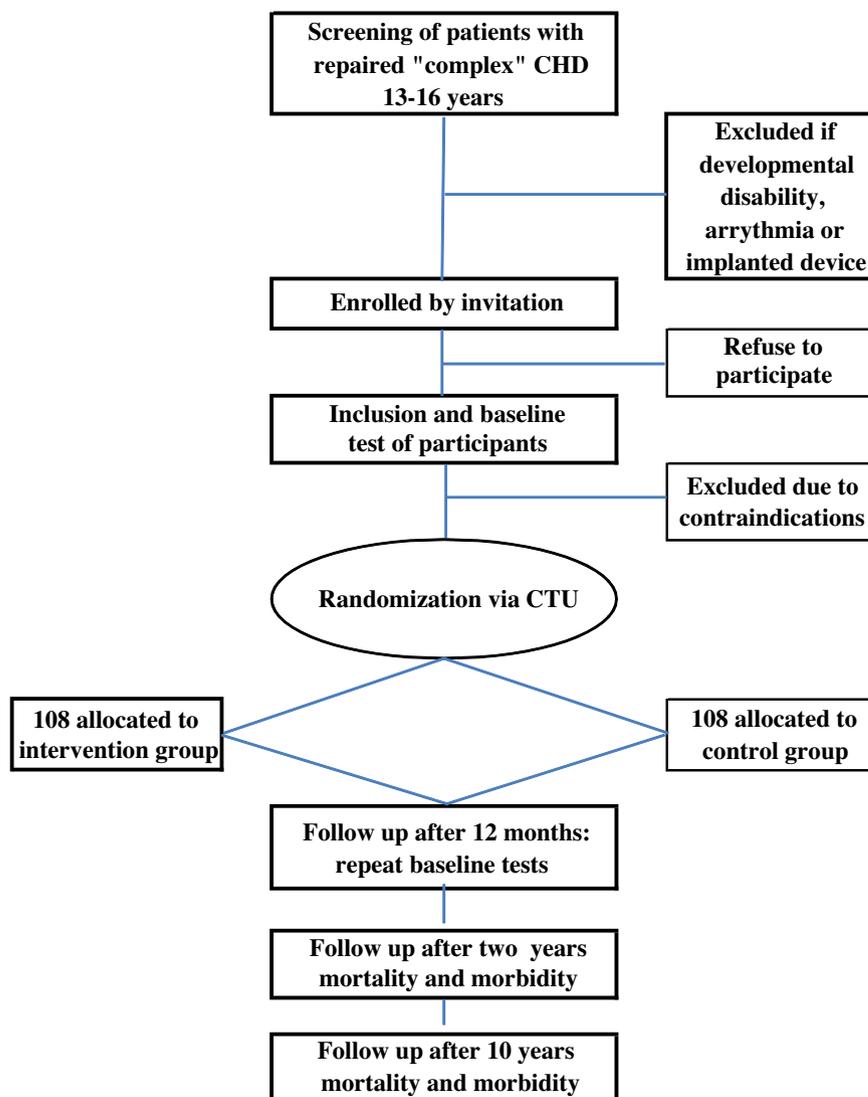
difference between the intervention group and the control groups in change in Watt max test from baseline to 12-month follow-up will amount to 13 W with a standard deviation of 34 W, as stated by Rhodes et al,¹¹ 108 are to be randomized to the experimental group. This means that we will be able to detect or refute an effect of the intervention in a randomized comparison at the size of the before- and after-difference measured in the group who carried out an exercise period in the study of Rhodes et al, assuming that the control group' Watt max does not change. The calculation is performed assuming normal distribution for the change for 1 year in the Watt max test. To detect or reject a 14% (13/93) improvement in Watt max test with a risk of type I error (α) of 5% and a risk of type II error (β) of 20% (power = $1 - \beta = 80\%$), $108 \times 2 = 216$ adolescents with CHD have to be included in the trial. For normally distributed data, a 2-way analysis of covariance will be undertaken on effect parameters (Group × Time), and for data, which do not fulfil the assumption of the parametric method after an appropriate logarithmic transformation, a Friedman test will be used (2-way analysis of variance). A multiple regression analysis of the change from baseline in the exercise test as a function of baseline variables will be made. It is to be analyzed if sex and self-rated health are significant predictors of the outcome. All data will be analyzed according to the intention-to-treat principle, and an unadjusted analysis as well as an analysis adjusted for design variables, including stratification variables, will be presented and discussed. A blinded statistician with no knowledge of the group allocation undertakes all statistical analysis. Primarily, the group of researchers will interpret the results, and the main conclusions of the trial are made before the de-masking of the group allocation takes place (Figure 2, flowchart).

Ethical considerations

The Danish Data Protection Agency (2007-58-0015) and the Regional Ethics Committee approved the trial protocol (H-1-2010-025), which qualified for registration in the ClinicalTrials.gov, number identifier: NCT01189981.

The rationale for providing health education as a standard intervention is, first and foremost, due to ethics reasons with reference to the Helsinki Declaration as well as the Convention on the Rights of the Child (United Nations International Children's Emergency Fund 1989), saying that patients participating in research should not provide data for the sake of the research project but gain personal benefits.^{26,27} Second, the health education serves as a kickoff for individual planning of physical activity in the following year—with or without motivational support by the intervention program MinPuls.nu.

Figure 2



Flowchart. CHD indicates congenital heart defect; CTU, Copenhagen Trial Unit.

Informed consent

A cardiologist from one of the specialist centers evaluates all the eligible participants before contact. A letter from the research team, containing leaflet and participant information, is sent to all eligible participants. A follow-up telephone call is performed 10 days after the letter has been sent to the family, and the parents and the adolescent are given a verbal description of the trial. A supplementary letter is sent in case the family does not reply or cannot be reached by telephone. The participants and their parents must give

their written informed consent before the adolescent can participate in the trial.

Randomization

The centralized randomization takes place 10 days after the baseline test, when the Actigraph data have been collected. We use concealed allocation and adequate computer-generated allocation sequence to avoid selection bias. Thus, neither investigators and patients nor parents can influence which groups the

patients are allocated to. The patients are randomized using the stratification variables high/low VO_2 level at baseline and sex, to ensure balanced representation of participants with these prognostic variables in each group. Copenhagen Trial Unit undertakes the randomization using central telephone randomization.³¹

Strata is as follows: girls and boys and high/low VO_2 peak: high VO_2 -peak girls $>35.9 \text{ mL min}^{-1} \text{ kg}^{-1}$ and high VO_2 -peak boys $>45.9 \text{ mL min}^{-1} \text{ kg}^{-1}$. High/low values were determined based on research with Scandinavian adolescents with CHD in a similar age category.⁹

Allocation to the trial began in October 2010 and is planned to stop October 2012. Data collection ends October 2013, and results are expected after October 2014. A 2- and 10-year follow-up on mortality and morbidity will take place by register studies.

The trial is expected to contribute with new knowledge regarding whether physical activity improves health and, if so, how physical activity can be increased and possibly comorbidity reduced in adolescents with CHD.

Conclusion

A randomized clinical trial is undertaken to test whether a 1-year Internet, mobile application, and SMS-based program to encourage increased exercise results in better aerobic fitness. The chosen method seems applicable and feasible to adolescents with CHD. The trial is expected to contribute with new knowledge regarding whether physical activity in participants with CHD can be increased and, possibly, comorbidity be reduced.

Disclosures

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Paper II

Full title: Effects of eHealth encouragements to physical activity in adolescents with congenital heart disease: The PReVaiL randomized clinical trial.

In review

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ABSTRACT

Objective To assess benefit and harms of adding an eHealth intervention to health education and individual counselling in adolescents with congenital heart disease; The PReVail Trial

Design Randomized clinical trial

Setting Denmark

Patients A total of 158 adolescents aged 13-16 years with no physical activity restrictions after repaired complex congenital heart disease

Interventions PReVaiL consisted of individually tailored eHealth encouragement physical activity for 52 weeks. All patients received 45 minutes of group-based health education and 15 minutes of individual counselling involving patients' parents.

Outcomes The primary outcome was maximal oxygen uptake (VO₂ peak) at 52 weeks after randomisation, which was assessed by an incremental cardiorespiratory exercise test performed on a bicycle ergometer to exhaustion. The secondary outcome was physical activity assessed by accelerometry. Exploratory outcomes were generic and disease-specific questionnaires assessing health-related quality of life.

Results In the intervention group, 58 (72%) patients completed the final test, but of those only 46 (57%) fulfilled the compliance criteria of using the eHealth application for at least 2 consecutive weeks. In the control group, 61 (79%) patients completed both exercise tests. Adjusted for baseline values, the difference between the intervention group and the control group in mean VO₂ peak at one year was $-0.65 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (95% CI -2.66 to 1.36). Between-group differences at one year in physical activity, generic health-related quality of life, and disease-specific quality of life were not statistically significant.

Conclusions Adding an tailored eHealth intervention to health education and individual counselling did not affect outcomes among adolescents with congenital heart disease. Our results do not support the use of this eHealth intervention in adolescents with complex congenital heart disease.

Trial registration: Clinical trials.gov identifier: NCT01189981

Conflict of Interest: All authors declare they have no conflicts of interest

Keywords: Heart Defects, Congenital; Adolescent; Exercise; eHealth

INTRODUCTION

Cardiorespiratory fitness, measured as maximal oxygen uptake VO_2 , is an important predictor of morbidity and mortality.(1) Adolescents and adults with congenital heart disease (CHD) have lower VO_2 than healthy individuals.(2-4) Although structural heart abnormalities partly explain this discrepancy, low levels of physical activity among patients with CHD may contribute to the overarching problem.(5) Physical activity counselling in adolescent heart patients seems to be underused, presumably due to logistic problems, expense, and parental anxiety about adverse events.(6)

Home- or facility-based exercise training programmes may improve VO_2 in patients with CHD.(7;8) However, methodological limitations of high risks of systematic error, random error, and design errors hamper the internal validity of previous studies.(8-10) Thus, no evidence-based guidelines exist regarding the most effective way to encourage adolescents with CHD to be more physically active.

The prevalence of CHD is increasing worldwide,(11) and there is a resulting need to assess the effects of rehabilitation programmes that can safely and inexpensively connect with adolescents, including those geographically distant from specialist centres.(12) The potential of eHealth—health services and information delivered or supported through the Internet and related technologies(13)—is largely unexplored in this group of patients. Our objective was to assess the effect of adding a home-based eHealth intervention to health education and individual counselling among adolescents with CHD.

METHODS

Design

The Paediatric Rehabilitation for Vanguard in Lifeskills (PReVaiL) trial was a nationwide, parallel group, randomized clinical trial conducted in Denmark between 2010 and 2014. The trial protocol was published before randomising patients.(14) Deviations from the original protocol were approved by the Regional Ethics Committee trial protocol H-1-2010-025 and applied to the ClinicalTrials.gov identifier. Protocol changes addressed an insufficient inclusion rate and minimally broadened inclusion criteria, adding patients with other congenital heart diagnoses and those with forced expiratory volume (FeV1) \leq of expected 80% after indications of asthma were excluded. The trial conformed to the CONSORT criteria for research on e-Health intervention and

adhered to the framework for complex interventions described by the Medical Research Council.(15;16)

Eligibility and inclusion

Patients were identified from the Danish National Register of Patients. Inclusion criteria were: age between 13 and 16 years, previous repair for a complex CHD, and assignment to lifelong medical follow up.(14) Complex CHD was defined as: “vulnerable to additional acquired co-morbidities that impact both their cardiac and medical care, including hypertension, pulmonary, renal, and myocardial disease, and coronary artery disease”.(17, p.1171) Exclusion criteria were significant residual defects and physical activity restrictions. Patient health records were manually checked for clinically important co-morbidities that could lead to exclusion (Table 1).

Eligibility to participate was confirmed by each patient’s cardiologist. Eligible patients were contacted between May 2010 and May 2013 by a letter providing information about the trial and soliciting participation. Two weeks later, eligible patients’ parents were contacted by telephone; with their approval, study staff also spoke by phone with adolescents to know if they would participate. All trial information was repeated at the test site before study inclusion. Parents and adolescents were then asked to provide signed consent (Figure 1).

Randomization

The randomization was performed by the Copenhagen Trial Unit ten days after the baseline test.(18;19) A trial investigator centrally randomized eligible patients 1:1. The computer-generated allocation sequence used permuted blocks with varying sizes of 6, 8, or 10. The allocation sequence and block size were unknown to the trial investigators. Patients were stratified according to gender and high or low VO₂ peak, using age-matched Scandinavian adolescents with similar cardiac diagnoses.(20) High VO₂ peak in girls was defined as greater than 35.9 ml*kg⁻¹*min⁻¹. High VO₂ peak in boys was defined as greater than 45.9 ml*kg⁻¹*min⁻¹

Trial settings

All tests were performed at the Institute of Sports Medicine in Copenhagen by a team consisting of three nurses, a health coach specialising in adolescence, and two exercise physiologists. The team was blinded to the group allocation of patients.

Interventions

All patients received 45 minutes of group health education and 15 minutes of individual counselling with their parents. Health education and individual counselling was provided in

compliance with the Helsinki Declaration and the UNICEF Convention on the Rights of the Child, which decree that patients participating in research should gain personal benefits.(21;22)

The goal of the health education was to stimulate sources of self-efficacy before baseline tests. Inspired by Bandura's Social Cognitive Theory, health education was provided to small groups of same-gender adolescents (23); the curriculum covered physical activity, smoking, alcohol, diet, and sleep. In the group setting, patients shared experiences with physical activity and other incidental experiences. The individual coaching was intended to reinforce patients' perceived competence after baseline tests and action planning based on health education and personal preferences. Behaviour change techniques applied in the intervention included: 1) information on benefits of physical activity, 2) goal setting, 3) action planning, 4) barrier identification and problem solving, 5) setting of graded tasks, 6) environmental structuring, 7) facilitation of social comparison, 8) time management, and 9) stimulation of future rewards.(24)

The experimental intervention

The experimental intervention consisted of a 52-week Internet, mobile application, and SMS-based programme delivering individually tailored text messages to encourage physical activity. The intervention was feasibility tested and concurrently adapted by the software developer(14). The programme encompassed three main approaches: health education, tailored interactive text encouragements, and a personal exercise planning tool.

Text messages encouraged short term activities with at least 10 minutes of high intensity as often as possible throughout the day. High intensity was defined for the patients as physical exertion leading to increased heart rate and respiration. The programme adhered to guidelines for healthy adolescents that recommend being physically active for at least 60 minutes per day. The activity should be of moderate to high intensity and should extend beyond the usual short-term daily activities. If the 60 minutes were divided, each activity should last 10 minutes or more.(25) The patients allocated to the eHealth intervention were sent health information and a new encouragement every week. Examples of such encouragements could, e.g., be "the challenge this week is that you must run the longest trip you've ever run" or "try to see how long you can keep yourself going".

Patients recorded exercise duration and type in a mobile application that translated intensity into virtual points, a system designed to provide motivation. The mobile application could also be used to plan and register all other activities during the day. The patients could monitor their results

on a personal website, with a goal of achieving a bronze, silver, or gold level of points on a weekly basis. The intervention did not allow for interaction between patients due to concerns regarding safeguarding minors on the Internet. We used an existing and widely used eHealth platform, Mobile Fitness A/S Copenhagen, Denmark.(26)

Behaviour change techniques applied to the eHealth intervention were: 1) action planning tools, 2) rewards for successful behaviour, 3) self-monitoring of behaviour, 4) feedback on performance, and 5) demonstration of selected behaviours delivered as short videos via the mobile phone.(24)

Adherence to the intervention

Adherence to the eHealth programme was assessed by patient registration of physical activities via the eHealth application for at least two consecutive weeks during the trial. The risk of adverse events from participating in the purposed trial was minimal. Patients were instructed to contact their usual health care providers if medical problems occurred.

Outcomes

Primary outcomes

Peak oxygen uptake, $VO_2 \text{ peak} = \text{mlO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, was assessed by an incremental cardiorespiratory exercise test performed on a bicycle ergometer, Monark Ergonomic 839E, Monark Exercise AB, Sweden.(14;27;28) After a 10-minute warm-up period, patients followed the incremental protocol starting at 20 watts (W) + 20W/ min for girls and 25W + 25W/ min for boys until volitional exhaustion. Patients were encouraged to maintain a cadence above 80 rounds per minute and to continue for as long as possible during the tests; equivalent levels of encouragement were provided during all exercise tests. To avoid any adverse events, patients did not have to meet specific criteria for achieving VO_2 peak during the tests. Instead, they were encouraged to stop when they felt exhausted or experienced adverse symptoms. The mean respiratory exchange ratio (RER) achieved during the tests was 1.3 (SD 0.1; range 1.0 –1.61) and the mean maximum heart rate (HRmax) achieved was 189 (SD 11.7; range 157-217), following exclusion of an outlier only reaching 102. These results indicate that efforts at or near the maximum were generally achieved, as criteria for achievement of peak oxygen uptake are usually considered a combination of volitional exhaustion, heart rate HR near maximum, and RER above a certain level, e.g. 1.1.(29) The protocol was designed to achieve exhaustion within 6-12 minutes, which was the case for 61 % of patients, with a mean time to exhaustion of 8.3 minutes (SD 1.9; range 4.1 to 13.3 minutes). All exercise tests were performed without adverse events. Peak oxygen uptake was defined as the highest value

obtained over a five-second averaging interval, using breath-by-breath measures. The term ‘peak’, rather than ‘maximal oxygen consumption’, acknowledges that it was the peak value achieved under the specific conditions, which is not necessarily the true maximum but was verified by the described criteria.

Secondary outcomes

Physical activity was assessed using a commercially available accelerometer: ActiGraph model 77146, Pensacola, FL. Patients were asked to wear the monitors, which were set to record at five-second epochs, on the left hip from 6AM to 10PM for two weekend days and four weekdays.⁽¹⁴⁾ Total minutes per day spent in moderate to vigorous physical activity (MVPA) were assessed using 2000 accelerometer cut-point counts per minute as the lower threshold of moderate-intensity activity.⁽³⁰⁾ Recordings of at least one weekend day and one weekday of at least 10 hours were defined as valid. Days with more than 10 hours of recordings that included periods where the accelerometer was not worn were adjusted to a full-day of 14 hours estimated awake time for this population.⁽³¹⁾

Physical activity was also assessed by an electronic questionnaire validated by the Health Behaviour of School-aged Children survey.⁽³²⁾ Acceptable reliability and validity have been reported. ⁽³³⁾

The investigator read the items to patients and recorded their responses. This took place in a separate room; patients’ parents were not present.

Exploratory outcomes

Health-related quality of life was assessed by the Danish version of the Paediatric Quality of Life Inventory questionnaire for teens ages 13-18 years, using the generic and the disease-specific version.⁽³⁴⁾ Good reliability and validity have been reported. ^(35;36) The generic module assessed four domains: physical functioning, emotional functioning, social functioning, and school functioning. The disease-specific module assessed six domains: heart problems and treatment, treatment II, perceived physical appearance, treatment anxiety, cognitive problems, and communication. The disease-specific questionnaire was translated into Danish and linguistically validated by six age-matched patients and 12 healthy adolescents.

Sample size estimation

Sample size was estimated based on existing research with adolescents with CHD.(10) Assuming a mean difference of 13 watts in the cardiorespiratory exercise test between the intervention group and the control group, a standard deviation of 34 watts, and a risk of Type I error of 5% and a risk of Type II error of 20%, we estimated that a total of 216 patients needed to be randomized.

Statistical analysis

Data were analysed using SPSS, version 20.0 and STATA version 13. The statistical analysis plan was published before access to data. The primary analyses for all continuous outcomes were analysis of covariance (ANCOVA), adjusted for VO₂ peak at baseline and for the stratification variables of gender and high/low exercise capacity. The primary analysis for all binary outcomes was a logistic regression adjusted for the stratification variables. The secondary analysis for all continuous outcomes was an ANCOVA adjusted for VO₂ peak at baseline, the stratification variables of gender and high/low exercise capacity, age at test years, lung function, muscle strength, and body composition. The secondary analysis for all binary outcomes was an unadjusted logistic regression. The tertiary analysis for all continuous outcomes was an ANCOVA adjusted for baseline values, stratification variables, and cluster association. The tertiary analysis for all binary outcomes was a logistic regression adjusted for the stratification variables and the cluster association.

Three populations were analysed. In the intention-to-treat population, multiple imputations were used to handle missing data.(37;38) The per-protocol population included all patients randomized to the intervention who recorded physical activities to the eHealth application in at least two consecutive weeks. The cluster population derived from a published cluster analysis on baseline health-related fitness variables associated with cardiorespiratory fitness, body composition, and muscle strength.(39) A statistician blinded to the intervention allocation performed all statistical analyses. The authors interpreted the results and formulated the main conclusions before the group allocation was revealed.

RESULTS

Flow of patients

We aimed to include 216 patients but were only able to include 158 patients because of lack of interest or active sports participation (Figure 1). Out of 560 adolescents assessed for eligibility, 66 girls and 92 boys were randomized to either the intervention group (n=81) or control group (n=77). The scheduled enrolment period was extended by six months due to slow recruitment. Of 158 enrolled patients, 119 (75%) completed both exercise tests; 58 (72%) of the test group and 61 (79%) from the control group.

Adherence to the intervention

Of 81 patients in the intervention group, just 46 (57%) patients used the eHealth application for at least two consecutive weeks, and completed both exercise tests. Only 8 (10%) patients were active users during the last week of the intervention. Just 57 (70%) of the patients in the intervention group, adhered to the intervention, using the eHealth application for at least two consecutive weeks. The 24 patients (30%) in the intervention group that did not actively use the eHealth application for at least 2 consecutive weeks during the one-year trial period were defined as not adhering to the protocol.

Baseline characteristics

Baseline characteristics were largely similar between the intervention and control groups (Table 2). Patients' mean age was 14.6 years (SD 1.3) at the time of baseline testing, and BMI was 21.2 (SD 3.6) among girls and 19.5 (SD 3.0) among boys. Average VO_2 among girls was 37.5 ml*kg⁻¹*min⁻¹ (SD 8.1) and among boys 47.9 ml*kg⁻¹*min⁻¹(SD 7.9). One third of all patients had had surgery for coarctation of aortae, 22% had had surgery for transposition of the great arteries, and 13% had had surgery for tetralogy of Steno-Fallot (Table 3).

Primary outcome

At one year, the mean VO_2 peak was 43.2 (SD 9.7) in the intervention group and 46.3 (SD 10.1) ml*kg⁻¹*min⁻¹ in the control group (Table 4). In the primary analysis adjusted for baseline VO_2 peak and stratification variables of gender and exercise capacity, the 95% CI of the difference in mean VO_2 peak between the intervention and control groups included zero and excluded a minimal relevant difference of 3 ml/kg/min. In the fully adjusted analysis, the difference in mean VO_2 peak between the intervention and control group of -0.41 (95% CI -2.45 to 1.63) included zero and excluded relevant difference. Subgroup analyses by gender and per-protocol recipients of the

intervention did not reveal statistically significant differences. The subgroup analysis adjusted for cluster allocation yielded similar results (not shown).

Secondary and exploratory outcomes

Patients in the intervention group spent a mean of 40.3 (SD 21.8) minutes per day in moderate to vigorous physical activity compared to 41.3 (22.9) minutes per day in the control group. The between-group difference of -.04 minutes day (95 %CI -2.23 to .23) was not significantly different. Assessments of physical activity by questionnaires yielded similar results. Differences in generic (0.32 points; 95%CI -2.39 to 3.14) and disease-specific health-related quality (-.72points ; 95%CI -3.73 to 2.89) of life between the intervention and control group were not significantly different.

DISCUSSION

Adding 52 weeks of eHealth encouragements to health education and individual counselling does not seem to increase physical fitness, physical activity, or health-related quality of life in adolescents with complex CHD.

Strengths

This trial has a number of strengths. The trial was conducted according to the CONSORT criteria, valid statistical methods were used, and there were only minor deviations from the pre-specified methodology, which was published in a protocol before randomization. Furthermore, multiple imputations were used to handle missing data decreasing the likelihood that the effect was affected by missing data under the assumption that data was missing at random. All tests were performed on the same site using the same equipment operated by the same team of experienced assessors, and validated tools measured VO₂, physical activity, and health related quality of life. The VO₂ was assessed by a bicycle ergometer test to exhaustion with breath-by-breath measurements of oxygen consumption and other respiratory variables, which increases internal validity. Finally, the intervention drew on an existing and widely used eHealth platform experienced in designing eHealth applications.(26)

Limitations

This trial also has a number of limitations. We were only able to randomize 158 patients out of the 216 originally planned, and only 119 (75%) patients completed the trial. Our sample size was estimated based on the standard deviation obtained from a watt max test in a small study with the

highest methodological quality existing at the time the protocol was written.(14) Using the observed standard deviation of the current trial, based on the more precise outcome of VO_2 , the necessary sample size to detect a clinically relevant difference of $3.00 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}$ would be 160 patients. The 95% confidence interval for effect on the primary outcome reported here was -2.66 to 1.36, excluding a clinically relevant effect. Finally, the blinding of outcome assessors cannot be fully ensured in behavioural interventions because patients may reveal their group assignment during testing. However, to minimize risk of bias we instructed all patients not to disclose their allocation prior to outcome testing.

Strengths and limitations in relation to other studies

Rehabilitation studies in adolescents with CHD tend to investigate patients with Fontan-type circulation.(40) However, patients with Fontan-type circulation are not representative of the total population of patients with CHD allocated to lifelong care. We included adolescents with no limitations to physical activity across multiple diagnoses, increasing the generalizability of our findings to adolescents with CHD in general. Although it is a relatively small trial, the PreVaiL trial is larger than comparable home-based trials.(41-43) The fraction of eligible patients who enrolled was higher (58%) than in similar trials (29 -36%).(41-43) Home-based training studies in adults with CHD found between-group differences in VO_2 after both 10 and 24 weeks of graded training.(42;43) Factors like the time frame of the intervention, the patient's baseline VO_2 status, and the trial design may have influenced the results. A central question is how to motivate adolescents with CHD to be physically active on a regular basis. Two trials that included educational and motivational strategies reported a short-term effect on physical activity in adolescents and children with CHD.(41;44) Still, no trial in adults, adolescents, or children with CHD has shown any long term effects of any type of activity encouragement on physical fitness, physical activity, or health-related quality of life.(45)

Implications for clinicians and policy makers

Interventions using eHealth are low cost, but adding this 52-week Internet, mobile application, and SMS-based programme delivering individually tailored text messages to encourage physical activity to health education and individual counselling does not seem to affect fitness, physical activity, and health related quality of life in adolescents with CHD. It is possible that more intensive interventions are needed in order to change behaviour in adolescents, or eHealth interventions might not generally benefit physical fitness and health related quality of life in

adolescents with CHD. Based on the present trial we suggest that future eHealth interventions should be thoroughly piloted, to avoid problems of recruitment and retention.

Unanswered questions and future research

Considering the amount of available funding in the Horizon 2020 programme directed toward eHealth in empowering citizens to manage their own health, (46) researchers should carefully consider which eHealth trials may be worth conducting as not to waste time and money. More evidence is needed about behavioural change strategies to inform health education and counselling.

CONCLUSION

Adding our tailored eHealth intervention to health education and individual counselling does not seem to have any effect in adolescents with congenital heart disease and the few experimental participants using this eHealth intervention possibly contributed to the lack of effect. Our results do not support the use of this 52-week Internet, mobile application, and SMS-based programme, delivering individually tailored text messages to encourage physical activity in adolescents with complex congenital heart disease.

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AUTHOR CONTRIBUTIONS

SHK, LLA, URM, LS and JW designed the project and revised the manuscript. JCJ, SHK, LLA, LS, VZ and JW analyzed and interpreted the data and revised the manuscript: JW is the guarantor. URM, KD and AK collected data and revised the manuscript. All authors approved the final version of the paper.

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Tables

Table 1. Inclusion and exclusion criteria with ICD-10 codes

Inclusion criteria:

- Corrected or palliated congenital heart disease with allowance for unrestricted exercise (NYHA 1)
- Diagnosis: Q20.0 Truncus arteriosus communis, Q20.1 Transpositio vasorum incompleta, Q20.3 Transpositio vasorum completa, Q20.5 Inversio ventriculorum cordis, Q21.2 Defectus septi atrioventriculorum cordis, Q21.3 Tetralogia Steno-Fallot, Q22.4 Tricusspidalatresia , Q22.5 Anomalia Ebstein, Q23.2 Mitralatresia, Double outlet right ventricle, Q23.3 Hypoplasia ventriculi sinistri cordis syndrome, Q23.3 Hypoplasia ventriculi dextrii cordis syndrome, Q24.4 Stenosis subaortae congenita, Q25.1 Coarctatio aortae, Q25.1 Coarctatio Aortae, Double inlet left ventricle, Q25.3 Stenosis aortae supraaortalis, Q25.5 Pulmonalatresia., Successful Total Cavo Pulmonal Connections (TCPC procedure)
- 13- 16 years of age during recruitment period

Exclusion Criteria:

- Mental retardation, or
- Untreated asthma, or
- Syndromes associated with congenital heart disease, or
- A systolic blood pressure >150 mm Hg measured on the right arm at the day of testing led to exclusion, and a request for a second opinion by the cardiologist in charge.

Abbreviations: NYHA, New York Heart Association

Table 2. Baseline characteristics of patients

	Interventio n group n = 81	Control group n = 77	Girls n = 66	Boys n = 92
Age, years, mean (SD)	14.6 (1.3)	14.6 (1.2)	14.5 (1.3)	14.6 (1.3)
Baseline anthropometrics, mean (SD)				
Height, cm	166 (10.4)	165 (9.5)	162 (6.6)	167 (11.2)
Weight, kg	57.0 (11.0)	58.0 (13.4)	57.9 (11.9)	56.8 (12.5)
BMI	20.0 (2.9)	20.5 (3.9)	21.2 (3.6)	19.5 (3.0)
Body surface area, m ²	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)
Waist, cm	72.0 (7.9)	73.0 (9.1)	71.3 (8.2)	73.4 (8.6)
Hip, cm	87.7 (8.6)	88.4 (10.6)	91.7 (9.8)	85.4 (8.6)

Waist/hip ratio	0.82 (0.1)	0.83 (0.1)	0.78 (0.1)	0.86 (0.1)
Sum of skinfolds, mm	13.3 (8.5)	12.5 (8.2)	17.8 (10.9)	9.4 (2.1)
Systolic BP, mm hg	119 (12.7)	118 (10.8)	116 (11.9)	120 (11.4)
Diastolic BP, mm hg	67.1 (6.6)	67 (6.7)	67.2 (5.5)	66.8 (7.4)
Resting pulse	69.2 (11.4)	71 (9.9)	70.8 (10.0)	69.6 (11.2)
Muscle strength, kg	29.1 (8.5)	27.9 (7.5)	26.1 (4.7)	30.2 (9.4)
Baseline lung function, mean (SD)				
Fev1/sec	3.0 (0.7)	3.0 (0.7)	2.7 (0.5)	3.2 (0.8)
Fev1/sec:% of predicted	94 % (0.1)	94 % (0.1)	96 % (0.1)	92 % (0.1)
Cardiorespiratory fitness, mean (SD)				
Maximal oxygen uptake	43.7 (9.8)	43.3 (9.3)	37.5 (8.1)	47.9 (7.9)
VO ₂ ml/min/kg				
HRR beats/min	122.8 (15.1)	122.0 (15.9)	121 (13.9)	120.7 (14.1)
Oxygen pulse	13.1 (3.3)	12.9 (3.6)	11.3 (1.9)	14.2 (3.8)
Max work load (Watt)	185 (48.1)	182 (46.6)	158 (26.6)	201 (50.6)
Anaerobic threshold	0.7 (0.2)	0.7 (0.1)	0.67 (0.2)	0.72 (0.1)
RER	1.3(0.1)	1.3 (0.1)	1.3 (0.1)	1.3 (0.1)
Physical activity, mean (SD)				
Time physical activity, minutes,	438 (159)	475 (176)	430 (178)	476 (159)
Minutes \geq 2000 counts,	45.8 (24.1)	49.8 (26.6)	43.0 (27.0)	51.3 (23.7)
Leisure time, days per week, hours	3.1 (0.7)	2.9 (0.2)	4.3 (1.5)	4.4 (1.5)
Sedentary time, week day, hours	3.2 (1.6)	3.2 (1.7)	3.1 (1.3)	3.9 (1.7)
Sedentary time, weekend day,	4.4 (1.9)	4.9 (1.9)	4.2 (1.5)	5.3 (1.9)

hours

MVPA \geq 60 minutes a day, percent of patients	32%	26%	18 %	34%
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Health-related quality of life, mean (SD)

Generic	80.0 (9.4)	80.4 (9.5)	78.9 (10.5)	81.3 (8.4%)
Disease-specific	85.2 (10.7)	84.6 (9.7)	82.6 (12.3)	86.6 (7.8)

Abbreviations: BMI, body mass index; Fev1, forced expiratory volume; HRR, heart rate reserve; RER, respiratory exchange ratio; MVPA, moderate vigorous physical activity

Table 3. Prevalence of congenital heart conditions, n (%)

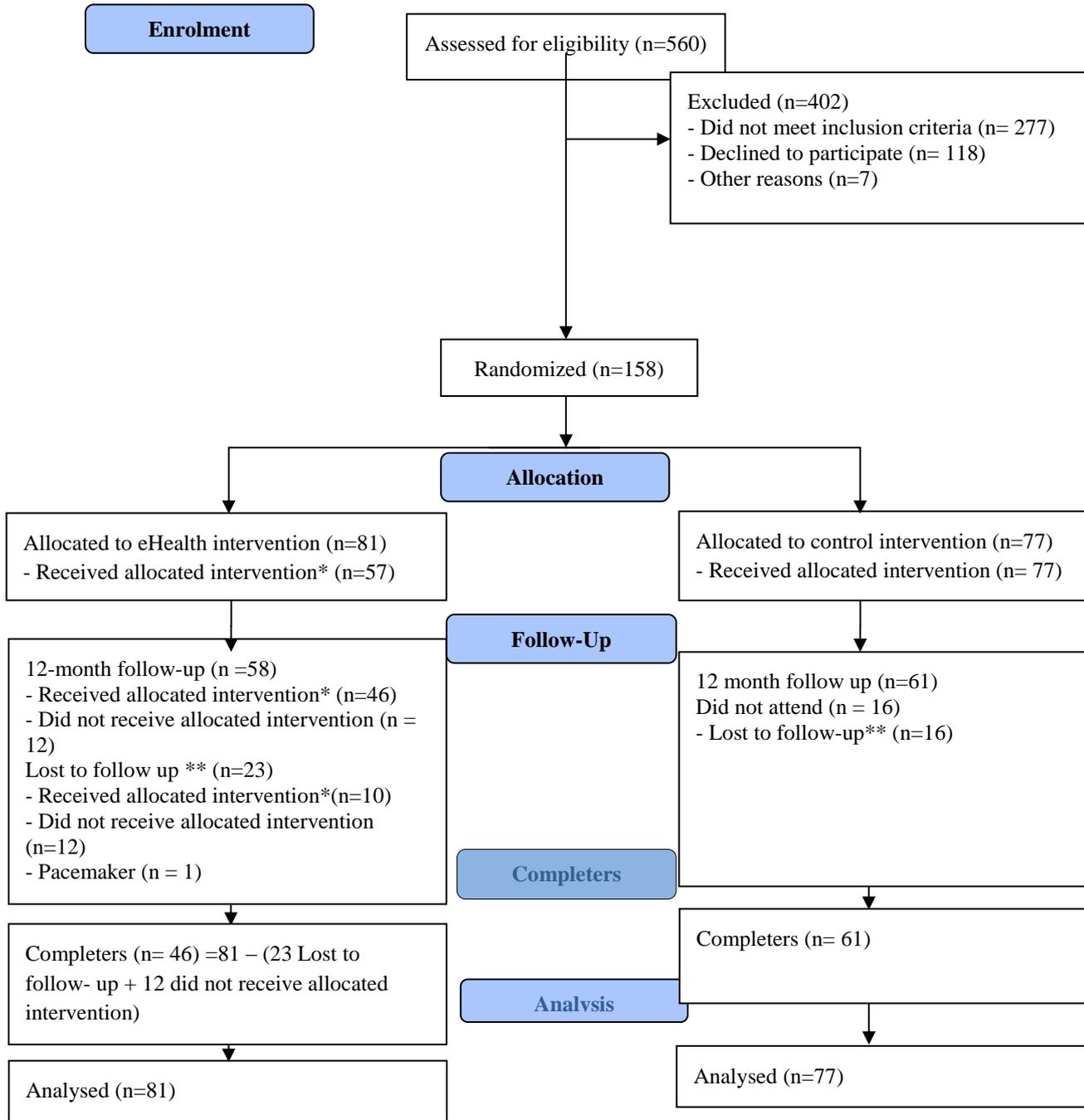
	All patients n = 158	Intervention group n =81	Control group n=77	Girls n=66	Boys n=92
Coarctation of the aorta	52 (33%)	31 (38%)	21 (27%)	19 (29%)	33 (36 %)
Transposition of the great arteries	35 (22%)	21 (26%)	14 (18%)	13 (20%)	22 (24 %)
Steno-Fallot tetralogy	21 (13%)	8 (10%)	13 (17%)	9 (14%)	12 (13 %)
Double outlet right ventricle	7 (4%)	4 (5%)	3 (4%)	4 (6 %)	3 (3%)
Truncus arteriosus	4 (3%)	3 (4%)	1 (1%)	2 (3%)	2 (3%)
Atrioventricular septal defect	9 (6%)	1 (1%)	8 (11%)	6 (9%)	3 (3 %)
Total cavopulmonary connection surgery	6 (4%)	2 (2 %)	4 (5 %)	2 (2%)	4 (4%)
Other	24 (15%)	11 (14%)	13 (17 %)	11 (17%)	13 (14%)

Table 4. Between-group differences at one year

	Intervention group n=81	Control group n=77	Between-group difference (95% CI)	P value
VO ₂ peak, mean (SD)	43.2 (9.7)	46.2 (10.1)	-0.65 (-2.66 to 1.36)	0.52
Girls	37.5 (7.4)	36.6 (7.9)	0.04 (-2.91 to 2.83)	0.98
Boys	47.8 (9.0)	50.9 (7.6)	-1.47 (-4.23 to 1.31)	0.30
Per protocol ^a	44.1 (10.3)	46.2 (10.1)	-.01 (-2.13 to 2.11)	0.99

a = The per-protocol population included all patients randomized to the intervention who recorded physical activities to the eHealth application in at least two consecutive weeks (n=57)

Figure 1. CONSORT diagram



* used the eHealth application for at least 2 consecutive weeks.

** Reasons for becoming lost to follow up included unwillingness to miss school for one day, upcoming exams, loss of interest, and no suitable dates available for appointments.

Paper III

Klausen SH, Wetterslev J, Sondergaard L, Andersen LL, Mikkelsen UR, Dideriksen K, et al.
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Original article

Health-Related Fitness Profiles in Adolescents With Complex Congenital Heart Disease



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A B S T R A C T

Purpose: This study investigates whether subgroups of different health-related fitness (HrF) profiles exist among girls and boys with complex congenital heart disease (ConHD) and how these are associated with lifestyle behaviors.

Methods: We measured the cardiorespiratory fitness, muscle strength, and body composition of 158 adolescents aged 13–16 years with previous surgery for a complex ConHD. Data on lifestyle behaviors were collected concomitantly between October 2010 and April 2013. A cluster analysis was conducted to identify profiles with similar HrF. For comparisons between clusters, multivariate analyses of covariance were used to test the differences in lifestyle behaviors.

Results: Three distinct profiles were formed: (1) *Robust* (43, 27%; 20 girls and 23 boys); (2) *Moderately Robust* (85, 54%; 37 girls and 48 boys); and (3) *Less robust* (30, 19%; 9 girls and 21 boys). The participants in the Robust clusters reported leading a physically active lifestyle and participants in the Less robust cluster reported leading a sedentary lifestyle. Diagnoses were evenly distributed between clusters.

Conclusions: The cluster analysis attributed some of the variability in cardiorespiratory fitness among adolescents with complex ConHD to lifestyle behaviors and physical activity. Profiling of HrF offers a valuable new option in the management of person-centered health promotion.

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IMPLICATIONS AND CONTRIBUTION

Profiling of health-related fitness and its relation to lifestyle behaviors offers a valuable new option in the management of person-centered health promotion among adolescents with complex congenital heart disease.

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The life expectancy of adolescents with congenital heart disease (ConHD) has improved substantially over recent decades [1]. Sixty years ago, approximately 90% of patients died before they reached adulthood; more than 90% now survive [2]. Illnesses once considered fatal have become chronic and patients' care needs are changing [3].

Physical activity is essential for adolescents with ConHD [4]. Despite existing recommendations of physical activity for patients with restrictions due to dysfunction of the heart and the great vessels [5], person-centered implementation strategies are still in the development phase [6].

Overweight due to inactivity adds to comorbidity in adolescents with ConHD [7], and one of the future challenges in clinical practice is to ensure meaningful promotion of physical activity [8]. Adolescents with ConHD whose activity is not restricted by their cardiac condition are generally recommended to adhere to public health physical activity recommendations [6]. Given that many healthy adolescents find it difficult to adhere to public health recommendations, there is reason to believe that this is also challenging for adolescents with ConHD.

Physical activity refers to leisure-time activity, occupational- and school-related activity, and exercise training and sports [9]. Physical activity is related in a complex way to health, morbidity, and mortality outcomes, and it has been suggested that physical activity interacts with health-related fitness (HrF) [10]. HrF includes cardiorespiratory fitness and is affected by environmental conditions, lifestyle behaviors, personal attributes, the physical and social environment, and heredity, as well as neurological and developmental abnormalities [9,11]. Thus, HrF is an important marker of individual health and well-being [12].

Cluster analysis allocates individuals into groups on the basis of selected shared characteristics; it has been used to examine associations between clusters of lifestyle behaviors in healthy adolescents and age, gender, and health outcomes [13]. The present study focuses on the reverse, namely, whether clustering of health outcomes is associated with lifestyle behaviors. To the best of our knowledge, no such associations have been reported among adolescents with ConHD. Consequently, the aim of this study was to use HrF profiles to identify clusters of adolescents with ConHD and examine if lifestyle behaviors differ between clusters.

Methods

Study population

A Danish nationwide sample was recruited by letter and consisted of 158 adolescents aged 13–16 years with complex ConHD, defined as follows: patients vulnerable to additional acquired comorbidities that impact their cardiac care and thus assigned to lifelong follow up at specialist centres [14]. All participants had no symptoms (New York Heart Association 1) [15] and were not subject to any restrictions on competitive sports [16].

Written informed consent was obtained from the adolescents and their parents.

Variables and measurement

HrF was assessed by the following components: cardiorespiratory fitness, muscle strength, and body composition. Cardiorespiratory fitness was measured using peak oxygen uptake (VO_2 peak = mL O_2 /kg/min), heart rate (HR) reserve (maximal HR–HR at rest), oxygen pulse (O_2 /HR = volume of oxygen consumed by the body per heartbeat), and Watt max (maximal workload sustained for 1 minute) during an incremental cardiopulmonary exercise test performed on a bicycle ergometer (Monark Ergo- medic 839E, Monark Exercise AB, Vansbro, Sweden). After 10 minutes warm up, the patient undergoes the Godfrey cycle

ergometer protocol to elicit a maximal oxygen uptake response. Muscle strength was measured as isometric hand grip strength in kilograms by a North Coast Hydraulic Dynamometer (PROcare, Roskilde, Denmark) and the highest of three values was recorded [17]. Body composition was measured by body mass index (BMI, kg/m²) and the sum in millimeters of skinfolds at four sites (biceps, triceps, subscapular, and suprailiac) [18].

Lifestyle behaviors were measured by questions validated by HBSC, a collaborative cross-national research study, monitoring various health and lifestyle determinants in school-aged children [19]. These were supplemented by questions, developed for adolescents with ConHD [20]. All items had five response categories. The mean score (range, 1–5) was used as a continuous. Baseline data were collected between October 2010 and March 2013. All tests were conducted by the same investigators at a single test site. All questionnaires were filled out electronically; parents were absent. The Danish Data Protection Agency (2007-58-0015) and the Regional Ethics Committee approved the trial protocol (H-1-2010-025) before enrollment of the first participant. Informed and signed consent was obtained from both the adolescents and their parents.

Statistical analysis

All statistical tests were performed in SPSS statistical software for Windows (20.0; SPSS Inc., Chicago IL). HrF variables were grouped into strongly interrelated profiles by a combination of hierarchical and nonhierarchical cluster analysis [21]. First, a hierarchical cluster analysis estimated the number of likely clusters by measuring the similarity within several cluster solutions by an agglomerative solution, Ward's method [22]. The similarity measure of Euclidean distances, which uses the error sum of squares and fuses the two clusters whose fusion results in the minimum increase in the error sum of squares, was applied [23]. Each participant's characteristics were then joined to the group where he or she added least to within-group variability. Three clusters appeared to be solid on the basis of multiple iterations, a dendrogram, and an elbow test [22]. Second, a nonhierarchical *k*-cluster analysis was used to produce the three clusters by placing each participant in the cluster that resulted in the smallest increase in the overall sum of squared within-cluster distances.

To detect any differences between clusters in relation to lifestyle behaviors, multivariate analyses of covariance were undertaken across several lifestyle variables. To control for Type I error due to multiple testing, only a significance level of .05 after Bonferroni correction was accepted.

Results

Three stable clusters represented 158 participants comprising 66 (41%) girls. The mean age of girls was 14.6 years (standard deviation [SD], ± 1.3); and the mean age of boys was 14.6 years (SD, ± 1.2). Mean oxygen uptake in girls and boys was 37.5 (± 8.1) and 47.9 (± 7.9), respectively. All tests were completed in concordance with guidelines and no tests were ended because of criteria for ending tests [24].

Cluster names were on the basis of the characteristics of the HrF variables that formed them. Cluster 1, Robust, included 43 participants, 27% of the total sample; this group of very fit and physically strong adolescents included 20 (47%) girls. Cluster 2, Moderately robust, included 85 participants, 54% of the total sample;

adolescents in this cluster, 37 (42%) of whom were girls, had a fitness level close to the mean of the total sample. Cluster 3, Less robust, included 30 participants, 19% of the total sample; these participants, nine (30%) of whom were girls, were categorized by a nonathletic body composition and lack of muscle strength.

Diagnoses were evenly distributed between clusters. The diagnoses of the 158 participants are shown in Appendix A. Of these participants, 52 (33%) were diagnosed with coarctation of the aorta, 35 (22%) were diagnosed with transposition of the great arteries, and 21 (13%) were diagnosed with tetralogy of Fallot. Fifty (32%) participants were diagnosed with various complex diagnoses.

Mean values for HrF are reported by cluster in Tables 1 and 2. Mean oxygen uptake differed significantly between clusters. Muscle strength differed between clusters, as did BMI among girls. The girls in the Less robust cluster had the lowest BMI among clusters but, paradoxically, the highest sum of skinfolds.

The analysis yielded useful information about differences in lifestyle behaviors between clusters among girls. The girls in the Robust cluster led physically active lifestyles, according to their statements of exercise-specific self-efficacy, exercise hours per week, enjoyment of physical activity, and physical competence compared with peers. The opposite was the case with the girls in the Less robust cluster, whose statements indicated that they led a sedentary lifestyle.

Mean values for lifestyle behaviors are reported in Table 3 and shown graphically by z scores in Figure 1. The boys reported no differences in lifestyle behaviors between clusters, apart from their enjoyment of physical activity. The boys in the Less robust cluster enjoyed physical activity less than the boys in the Robust cluster, yet boys reported no differences across clusters in exercise-specific self-efficacy, exercise hours per week, and physical competence compared with peers.

Discussion

Health-related fitness

Three distinct subgroups of HrF profiles were defined among girls and boys using cluster analysis: (1) Robust; (2) Moderately robust; and (3) Less robust. Lifestyle behaviors differed between clusters, primarily among girls. Among healthy adolescent girls, there is a decline in physical activity during adolescence [25] and a polarization of cardiorespiratory fitness [26]. Public health issues, in general, aim to promote physical activity in adolescent girls and there seem to be a need ensure this also takes place in clinical practice, with great attention to health education on physical activity and healthy lifestyle behaviors. Adolescence is a crucial period in life that brings multiple changes. It is important to promote physical activity in adolescence, because it is a period in life where physical activity and sedentary behavior patterns are established [27].

The HrF variables were analyzed for girls and boys separately to prevent cluster affiliations from being dominated by gender-specific body composition and muscle strength. Biological changes develop between the ages of 13 and 16 years, with increased testosterone production and increased muscle mass in boys and more fat deposits in girls [28]. The fact that differences in the profiles of girls and boys were present suggests the necessity for gender-specific health promotion [29].

It is important to note that HrF in adolescents with ConHD relates to the multiple demands of adolescence associated with physical growth, biological maturation, and behavioral development [30]. Boys evaluated their physical competence similarly across clusters, indicating that some may have overestimated their physical function, HrF, and physical activities. This finding confirms known gender differences in adolescents with ConHD

Table 1
Descriptive characteristics of the 66 adolescent girls related to profile; mean and SD

	Total; mean (SD)	Cluster 1 robust; mean (SD)	Cluster 2 moderately robust; mean (SD)	Cluster 3 less robust; mean (SD)	p values F test
	66	20	37	9	
Age (years)	14.6 (±1.3)	14.3 (1.1)	14.9 (±1.3)	14.0 (±1.2)	.061
Diagnoses [$\chi^2(0,780)$]; n					
TGA	13	4	7	2	
Steno Fallot	9	1	6	2	
CoA	19	8	9	2	
Other	25	7	15	3	
VO ₂ peak	37.5 (±8.1)	42.4 ^a (±7.8)	35.3 ^a (±7.1)	35.7 (±8.9)	.004
HRR	124.1 (±14.2)	129.2 ^b (±11.3)	124.6 (13.5)	106.6 ^b (±12.3)	.006
Oxygen pulse	11.3 (±1.9)	13.2 ^c (±1.5)	10.9 ^c (±1.8)	9.4 ^c (±1.2)	≤.001
Watt max	158.5 (±26.6)	187.7 ^c (±10.3)	153.3 ^c (±12.6)	113.9 ^c (±14.5)	≤.001
Hand grip strength	26.1 (±4.7)	26.7 ^d (±3.4)	27.2 (±4.2)	20.0 ^d (±4.3)	≤.001
BMI	21.2 (±3.6)	21.4 (±3.0)	21.8 (±4.0)	18.8 (±2.5)	.080
Sum of skinfolds	17.8 (±11.1)	15.7 (±8.9)	18.5 (±12.7)	19.3 (±7.4)	.592
RER	1.3 (±.1)	1.3 (±.1)	1.3 (±.1)	1.3 (±.1)	.828
AT	.7 (±.2)	.7 (±.1)	.7 (±.2)	.7 (±.1)	.651

Data are presented as mean (standard deviation) VO₂ peak = mL O₂/kg/min; HRR = heart rate reserve(max pulse–resting pulse); oxygen pulse = O₂/HR, volume of oxygen consumed by the body per heartbeat; Watt max (maximal workload/kg); hand grip strength (kg; body weight); BMI = body mass index(kg/m²); Sum of skinfolds measured at four sites: biceps, triceps, sub scapular, and suprilliac sites; RER = respiratory exchange ratio (the ratio of the amount of carbon dioxide produced to the amount of oxygen consumed or taken up); AT = anaerobic threshold (the exertion level between aerobic and anaerobic training).

CoA = coarctation of the aorta; SD = standard deviation; Steno Fallot = Fallots tetralogi; TGA = transposition of the great arteries.

Bonferroni post hoc tests include:

- ^a Significant differences between Cluster 1 and Cluster 2.
- ^b Significant differences between Cluster 1 and Cluster 3.
- ^c Significant differences between Cluster 1, Cluster 2, and Cluster 3.
- ^d Significant differences between Cluster 1 and Cluster 3.

Table 2
Descriptive characteristics of the 92 adolescent boys related to cluster solution; mean and SD

	Total; mean (SD)	Cluster 1 robust; mean (SD)	Cluster 2 moderately robust; mean (SD)	Cluster 3 less robust; mean (SD)	<i>p</i> values <i>F</i> test
	92	23	48	21	
Age (years)	14.6 (±1.2)	15.6 (±.9)	14.4 (±1.2)	13.8 (±1.0)	<.001
Diagnoses [$\chi^2(0,220)$]; <i>n</i>					
TGA	22	5	12	5	
Steno Fallot	12	2	6	4	
CoA	33	7	22	5	
Other	25	9	8	8	
VO ₂ peak	47.9 (±7.9)	52.3 ^c (±5.5)	48.2 ^d (±7.2)	42.4 ^{c,d} (±8.7)	≤.001
HRR	121.4 (±14.0)	134.6 ^{a,c} (±11.7)	118.1 ^a (±15.5)	114.7 ^c (±15.4)	≤.001
Oxygen pulse	14.2 (±3.7)	18.2 ^b (±3.4)	14.3 ^b (±2.1)	9.8 ^b (±1.4)	≤.001
Watt max	201.7 (±50.1)	267.4 ^b (±24.3)	199.7 ^b (±19.3)	134.5 ^b (±16.7)	≤.001
Hand grip strength	30.3 (±9.4)	40.9 ^b (±7.2)	29.4 ^b (±6.3)	20.9 ^b (±5.3)	≤.001
BMI	19.6 (±3.1)	20.9 ^c (±2.7)	19.8 ^d (±3.4)	17.7 ^{c,d} (±2.3)	.002
Sum of skinfolds	9.5 (±2.1)	10.3 ^c (±2.0)	9.7 ^d (±2.9)	7.9 ^{c,d} (±1.5)	.001
RER	1.3 (±.1)	1.3 (±.1)	1.3 (±.1)	1.3 (±.1)	.532
AT	.7 (±.1)	.7 (±.1)	.7 (±.2)	.7 (±.1)	.210

Data are presented as mean (standard deviation) VO₂ peak = mL O₂/kg/min; HRR = heart rate reserve (Max pulse – resting pulse); oxygen pulse = O₂/HR, volume of oxygen consumed by the body per heartbeat; Watt max (maximal workload/kg); hand grip strength (kg; body weight); BMI = kg/m²; sum of skinfolds measured at four sites: biceps, triceps, sub scapular, and suprilliac sites, RER = respiratory exchange ratio (the ratio of the amount of carbon dioxide produced to the amount of oxygen consumed or taken up); AT = anaerobic threshold (the exertion level between aerobic and anaerobic training).

CoA = coarctation of the aorta; SD = standard deviation; Steno Fallot = Fallots Tetralogi; TGA = transposition of the great arteries.

Bonferroni post hoc tests include:

- ^a Significant differences between Cluster 1 and Cluster 2.
- ^b Significant differences between Cluster 1, Cluster 2, and Cluster 3.
- ^c Significant differences between Cluster 1 and Cluster 3.
- ^d Significant differences between Cluster 2 and Cluster 3.

[28]. The present findings reflect these processes and provide a framework against which adolescents can evaluate their own physical activity status.

A strong physique and physical self-assurance, as displayed by the adolescents in the Robust cluster, may encourage some fit adolescents with ConHD to participate in extreme sports. A U-shaped relationship exists between weekly sports practice and

well-being in healthy adolescents [31]. Adolescents with a chronic condition appear to be attracted to risky behaviors at a greater rate than are healthy adolescents [32]. Therefore, counseling directed at Robust adolescents with ConHD should include discussing symptoms from extreme physical challenges that must not be ignored and information about an increased risk of poor well-being arising from excessive participation in sports.

Table 3
Differences in lifestyle behaviors between clusters

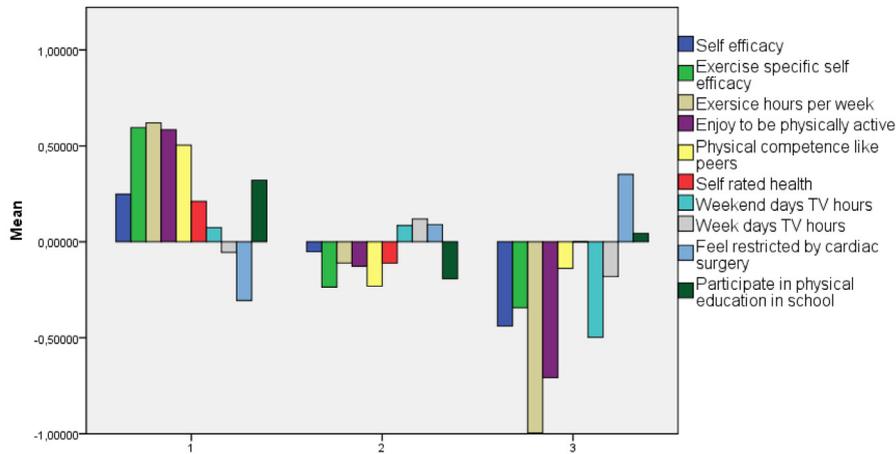
Variables	Total; mean (±standard deviation [SD])	Cluster 1 robust; mean (±SD)	Cluster 2 moderate robust; mean (±SD)	Cluster 3 less robust; mean (±SD)	<i>F</i>	<i>p</i>
Girls						
Self-efficacy	3.2 (.7)	3.4 (.5)	3.2 (.8)	2.9 (.6)	1.525	.226
Exercise-specific self-efficacy	62.3 (32.4)	81.6 (20.7)	54.9 (32.3)	51.4 (38.7)	5.505	.006*
Exercise hours per week	4.3 (1.5)	5.2 (.9)	4.1 (1.4)	2.8 (1.7)	11.037	≤.001*
Enjoy physical activity	4.1 (1.0)	4.7 (.7)	4.0 (.9)	3.4 (1.2)	6.736	.002*
Physical competence	3.0 (.9)	3.5 (1.0)	2.8 (.8)	2.8 (.9)	3.691	.031*
Self-rated health	3.0 (.8)	3.2 (1.0)	2.9 (.6)	3.0 (.9)	.626	.538
Weekend TV	4.2 (1.5)	4.3 (1.4)	4.3 (1.6)	3.4 (1.7)	1.311	.277
Week days TV	3.2 (1.3)	3.0 (1.2)	3.3 (1.3)	2.9 (1.3)	.416	.661
Feel restricted by heart surgery	1.6 (1.0)	1.3 (.9)	1.6 (.8)	1.9 (1.4)	1.596	.211
Participate in PE at school	4.6 (.8)	4.9 (.3)	4.4 (1.0)	4.7 (.5)	1.675	.196
Boys						
Self-efficacy	3.2 (.6)	3.3 (.5)	3.2 (.5)	3.0 (.6)	.613	.544
Exercise-specific self-efficacy	61.0 (21.0)	66.1 (16.0)	62.2 (21.0)	52.6 (23.6)	2.527	.086
Exercise hours per week	4.4 (1.5)	5.0 (1.4)	4.3 (1.4)	3.9 (1.9)	2.842	.064
Enjoy physical activity	4.2 (1.0)	4.5 (.6)	4.2 (1.0)	3.8 (1.2)	3.256	.043*
Physical competence	3.2 (.9)	3.4 (1.0)	3.2 (.9)	3.0 (.9)	.993	.375
Self-rated health	3.2 (.6)	3.2 (.5)	3.3 (.6)	3.0 (.6)	1.361	.262
Weekend TV	5.3 (1.9)	5.7 (1.9)	5.0 (1.8)	5.4 (2.1)	1.169	.348
Weekdays TV	3.9 (1.7)	3.6 (1.7)	4.0 (1.6)	4.1 (2.0)	.582	.561
Restricted by heart surgery	1.3 (.7)	1.1 (.5)	1.3 (.6)	1.5 (1.0)	1.784	.174
Participate in PE at school	4.6 (.9)	4.8 (.8)	4.6 (.9)	4.5 (.8)	.527	.517

PE = physical education.

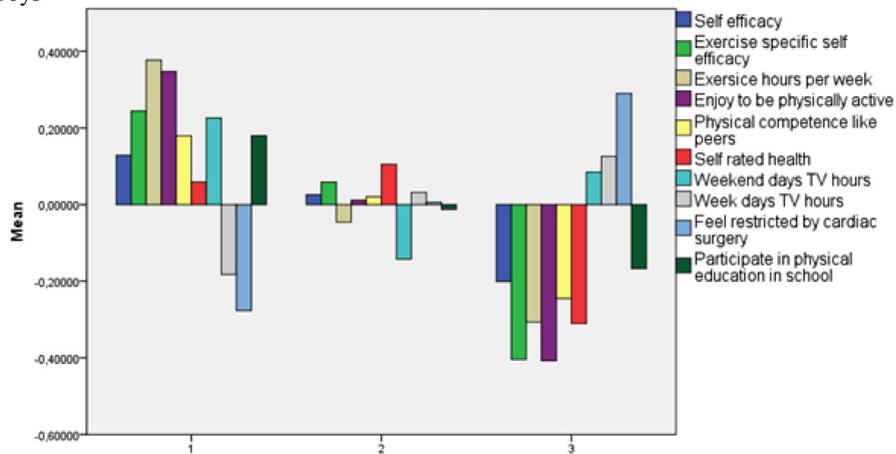
Self-rated health rated 1–4, self-efficacy and exercise-specific self-efficacy 1–100, physical education at school, physical competence, enjoy physical activity, restricted by heart surgery rated 1–5; Hours active leisure-time, Weekend and weekdays TV 0–7.

The significance value **p* < .5 after Bonferroni correction between clusters after multivariate analyses of covariance.

Girls



Boys



- 1 = Cluster 1, Robust
 2 = Cluster 2, Moderately Robust
 3 = Cluster 3, Less Robust

Figure 1. Differences in lifestyle behaviors between clusters, z scores.

Despite an overall physical and psychosocial health status similar to that of the general population, many children and adolescents with ConHD may suffer from developmental delays and spinal malformations [33]. Furthermore, developmental delays and limitations in motor skills have been described as common in children with ConHD from the age of 3 years [34]. Neurological deficits after uncomplicated surgery have been demonstrated at 1- and 4-year follow-up periods [35]. In addition, the risk of developing scoliosis after congenital heart surgery is more than 10 times the risk of developing idiopathic scoliosis [36]. Consequently, screening for developmental milestones, motor skills, neurological deficits, and scoliosis from a very young age could help identify individual strengths and hindrances in relation to physical activity.

VO₂ peak is a predictor of all-cause mortality in patients with ConHD [37]. Therefore, VO₂ peak is an important outcome for

observational and intervention studies in patients with ConHD. VO₂ peak is also associated with diagnosis, even when patients are asymptomatic [38]. This is in concordance with recent recommendations to evaluate hemodynamic and electrophysiologic variables, rather than diagnoses and specific defects, before tailored counseling for physical activities [5]. In the present study, VO₂ peak differed significantly between clusters, possibly influenced by physical activity. Patients' lifestyle behaviors and preferences may play a substantial role in the adoption of counseling recommendations. These factors are not a part of personalized assessments, yet successful implementation may depend on them [6].

The mean weight in the three clusters are within normal values for the age group, the mean values from participants in Clusters 1 and 2 following the same percentile, which for the girls are +1SD and for the boys are at the 50 percentile.

However, mean BMI in participants in Cluster 3 in both genders were approximately -1 SD below the two other clusters; the girls coming down to the 50% percentile and the boys coming down to -1 SD. In addition to lifestyle behaviors these findings may represent both biological/and genetic characteristics [39]. Despite a BMI within normal values the girls in Cluster 3 display high risk profiles due to sedentary behavior, lack of muscle mass and increased fat, as seen in healthy girls [13]. Future research may benefit from evaluating genetic differences and determinants for trainability in this population.

Knowledge of existing profiles of HrF among adolescents with ConHD can be useful for two reasons. First, it may aid in identifying modifiable markers of robustness and assessing individual risks related to confident, unmotivated, or reluctant attitudes regarding physical activity. Second, it calls into question whether promotion of physical activity will have the same effect on all adolescents with ConHD whose activity is not medically restricted.

Strengths and limitations

A strength of this study is that it has the potential to explain variability in HrF among a sample of adolescents whose physical activity is not restricted in for medical reasons. The different HrF profiles in girls and boys point to important lifestyle concerns that should be addressed in clinical care settings. Also, the study contributes to a broader view of health promotion in adolescents with ConHD.

Furthermore, the data are baseline data from the PREVAIL trial, and the cluster analysis was performed before the data at the end of the intervention period were gathered [40]. Therefore, we will be able to analyze whether a person belonging to one cluster compared with belonging to one of the other cluster will impact the effect of the incentive to increase physical activity. That is, whether there is an interaction between the intervention used in the PREVAIL trial and the sub grouping according to clusters determined in this study. The adjustment of the intervention effect for cluster may be a more wise way to exploit data to show whether the intervention effect is associated with known and unknown confounders as the cluster analysis integrates several possible confounders into one more operational covariate being membership of one of the clusters.

This study has several limitations. First, cluster analysis is an empirical data-driven approach, and outcomes are contingent on measures and sample characteristics. A relatively small body of statistical evidence supports cluster analysis, which is an exploratory classification method in which different clustering algorithms produce different results. Therefore, replication of the existence of three subprofiles of HrF on a different sample would be useful. Second, profiling could have been made more complete by including the HrF components of motor skills and metabolic profiles, which would have made possible associations with cardiovascular risk profiles in adulthood. Third, data were obtained from a small and relatively homogeneous sample; a larger sample could test the validity of the findings in this preliminary investigation. Fourth, the cluster technique may be perplexing because it does not differentiate between predictive and dependent variables.

Cluster analysis has been used in studies of healthy adolescents to classify health-related behaviors and categorize their lifestyles. This technique adds valuable information about lifestyle, physique, and robustness in adolescents in ConHD.

Profiling adolescents with ConHD could be the first step in the development of person-centered rehabilitation and prevention strategies.

The cluster analysis attributed some of the variability in cardiorespiratory fitness among adolescents with ConHD to lifestyle behaviors and physical confidence. Profiling of HrF offers a valuable new option in the management of person-centered health promotion. The cluster analysis revealed that some variability in HrF among adolescents with ConHD was unrelated to diagnoses. Girls and boys display dissimilar profiles, and more gender-specific research is needed to tailor health recommendations. Consequently, HrF profiling may be a first step in developing person-centered rehabilitation and prevention strategies for clinical practice.

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Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jadohealth.2014.11.021>.

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