Dissertation zur Erlangung des Doktorgrades
der Fakultät für Sport- und Gesundheitswissenschaften
der Technischen Universität München

A web-based exercise approach to improve functional outcomes in patients with congenital heart disease

von

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Aus Sasbach, Deutschland

2020

TECHNISCHE UNIVERSITÄT MÜNCHEN

Lehrstuhl für Präventive Pädiatrie
Fakultät für Sport- und Gesundheitswissenschaften

Klinik für angeborene Herzfehler und Kinderkardiologie
Deutsches Herzzentrum München

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Vollständiger Abdruck der von der Fakultät der Sport- und Gesundheitswissenschaften der Technischen Universität München zur Erlangung des akademischen Grades eines

Doktors der Philosophie (Dr. phil.)

genehmigten Dissertation.

Vorsitzender:
Prof. Dr. Thomas Horstmann

Prüfer der Dissertation:
1. Prof. Dr. Renate Oberhoffer-Fritz
2. Prof. Guido Pieles, Ph.D.

Die Dissertation wurde am 28.12.2020 bei der Technischen Universität München eingereicht und durch die Fakultät für Sport- und Gesundheitswissenschaften am 24.06.2021 angenommen.

ACKNOWLEDGMENT

This work was carried out from January 2018 to December 2020 under the guidance of Prof. Dr. Renate Oberhoffer-Fritz at the Department of Pediatric Cardiology and Congenital Heart Disease, in the German Heart Centre Munich of the Technical University Munich.

I first want to express my appreciation to PD. Dr. Jan Müller, who gave me the extraordinary opportunity to do my dissertation in his group, and for his invaluable guidance, constant encouragement, support, and constructive criticism during the whole course of my scientific research.

I am also very grateful to Prof. Dr. Renate Oberhoffer-Fritz for the supervision and the opportunity to be part of her wonderful team at the Institute of Preventive Pediatrics. Thank you very much for your support with important professional advice, but also many helpful comments and suggestions, and last but not least your trust in my work as staff during my time at your institute.

I really would like to thank my mentor Prof. Dr. Alfred Hager for letting me share his immense knowledge and experience in the field of congenital heart defects and for the unique opportunity of being part of his CPET lab.

I am also very grateful to Prof. Guido Pieles, Ph.D. for being my second referee for this thesis, and for all the interesting conversations we have had.

For funding, I would like to thank the Robert-Enke-Stiftung, Fördergemeinschaft Deutsche Kinderherzen e.V. and the Förderverein Deutsches Herzzentrum München.

I would like to thank Sabine Kesting, Meike Simon, and Leon Brudy for the careful proofreading of this manuscript.

A special thanks to my colleagues Leon Brudy, Celina Fritz, Julia Hock, Sebastian Freillinger, Julia Remmele. It was a pleasure to work with you, discuss with you, and share lots of happy moments inside and outside the work at the German Heart Center. I will always keep Leon's wise words in my mind. Thank you, that there were always special words for special moments. I thank all past and present members whom I have met at the German Heart Center as well as at the Institute of Preventive Pediatrics, for their kindness and their help.

At this point, I would also like to thank my former colleague Dominik Gaser for the many great memories during and after our time together at the Institute. Special thanks also to Tobias Engl, for helping with countless things that make everyday life so much easier.

I thank the Master students Anna Schoberer and Laura Willinger for their excellent contributions in the daily work with the patients.

I would also like to thank the entire team of the pediatric outpatient clinic, including nurses and doctors for their support and good cooperation in their daily work. However, my research would not have been possible without the participation and commitment of the children as well as their parents. Thank you so much for all the efforts with the training and for making the way to Munich several times for the re-evaluations.

Last but not least, I would like to thank my family and friends, especially the Finisher, for their support throughout my studies and my dissertation and their continuous encouragement. Finally, I would like to say a special thanks to Meike for her love, support, and most of all patience with me.

"Es ist nicht genug zu wissen, man muss auch anwenden;
es ist nicht genug zu wollen, man muss auch tun"

-Johann Wolfgang von Goethe-

To my family

Summary

Congenital heart disease (CHD) is the most common malformation in all life births of the human organism worldwide. Due to improved medical experience and treatments in pediatric cardiology over the past 70 years, a majority of almost 95% nowadays reaches adulthood. Even if survival is not the main issue in the treatment anymore, these patients still experience serious and noticeable sequels in the long-term. Children with CHD can suffer from motor deficits. These can persist into adulthood and also limit psychosocial aspects such as health-related quality of life.

In this dissertation, the aim was to improve both motor skills and quality of life in pediatric patients with CHD using a 24-week web-based exercise intervention. Three internationally published scientific articles contributed to the generated findings presented in the following.

A systematic literature review revealed that home-based exercise interventions are safe feasible and a useful alternative to supervised cardiac rehabilitation for all age groups of patients with CHD. Most studies lacked appropriate reporting of adherence and compliance.

Prior to the start of the intervention, preliminary methodological considerations on conducting the study were published and additionally registered in a clinical trial registry.

Health-related physical fitness and quality of life in children and adolescents with moderate or complex CHD could not be improved sufficiently. However, our 24-week web-based exercise intervention was feasible and no further adverse events could have been detected. The digital tracking used in the intervention platform, reliably reproduced adherence and compliance to the exercise training. Despite regular reminders, using emails or phone calls, appropriate training participation could not be achieved.

Nevertheless, efforts to develop eHealth approaches, that can be used for the individualized rehabilitation of pediatric patients with CHD, should be further intensified. Future studies should continue to examine digital approaches that use more gamified content with a playful character. Ideally, the whole family and peers such as friends or other children and adolescents, who have to cope with the same limitations, could be involved to motivate for regular exercise and improve motor skills and quality of life for this patient group.

Zusammenfassung

Angeborene Herzfehler (AHF) sind unter Lebendgeburten die weltweit häufigste Fehlbildung eines Organs. Aufgrund der medizinischen Erfahrungen und Behandlungsmöglichkeiten der letzten 70 Jahre, in der pädiatrischen Kardiologie, erreichen heutzutage 95% der Kinder mit AHF das Erwachsenenalter. Auch wenn bei der Behandlung nicht mehr nur das reine Überleben im Vordergrund steht, erfahren diese Patienten langfristig immer noch gravierende und einschneidende Einschränkungen. Kinder mit AHF können unter motorischen Defiziten leiden. Diese können bis ins Erwachsenenalter bestehen bleiben und auch psychosoziale Aspekte wie die gesundheitsbezogene Lebensqualität einschränken.

Diese Dissertation hatte zum Ziel sowohl die motorischen Fähigkeiten als auch die Lebensqualität bei pädiatrischen Patienten mit AHF durch eine 24-wöchige webbasierte Trainingsintervention zu verbessern. Drei international veröffentlichte wissenschaftliche Artikel trugen zu den nachfolgend vorgestellten Ergebnissen bei.

Eine systematische Literaturübersichtsarbeit zeigte, dass häusliche Trainingsinterventionen sicher durchführbar und eine nützliche Alternative zu betreuten kardialen Rehabilitationen für Patienten mit AHF jeglichen Alters sind. In den meisten Studien fehlen eine angemessene Dokumentation und ein Bericht über das Einhalten und Befolgen des geforderten Trainingspensums.

Vor Beginn der Intervention wurden vorläufige methodische Überlegungen zur Durchführung der Studie veröffentlicht und zusätzlich in einem Register für klinische Studien registriert.

Die gesundheitsbezogene körperliche Fitness und Lebensqualität bei Kindern und Jugendlichen mit moderatem oder komplexem AHF konnten nicht entscheidend verbessert werden. Dennoch war die 24-wöchige webbasierte Trainingsintervention umsetzbar und es traten keine weiteren unerwünschten Zwischenfälle auf. Die in der Interventionsplattform verwendete digitale Nachverfolgung ermöglichte es zudem, die Einhaltung und Befolgung des Trainingsprogrammes zuverlässig zu dokumentieren. Trotz regelmäßiger Erinnerungen per E-Mail oder Telefonanruf konnte keine ausreichende Trainingsbeteiligung erreicht werden.

Dennoch sollten Bestrebungen nach eHealth-Ansätzen, die für die individualisierte Rehabilitation von pädiatrischen Patienten mit AHF genutzt werden können, weiter intensiviert werden. Zukünftige Studien sollten weiterhin digitale Ansätze untersuchen, die mehr gamifizierte Inhalte mit spielerischem Charakter verwenden. Im Idealfall könnten die ganze Familie und Gleichaltrige, wie Freunde oder andere Kinder und Jugendliche, die mit den gleichen Einschränkungen zu kämpfen haben, einbezogen werden, um so die die Motivation für regelmäßiges Training zu steigern und die motorischen Fähigkeiten und die Lebensqualität dieser Patientengruppe zu verbessern.

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I. Abbreviations

6MWD	six minute walking distance
6MWT	six minute walk test
ACHD	adult congenital heart disease
AS	aortic valve stenosis
ASD	artrial septal defect
AVSD	atrioventricular septal defect
BP	blood pressure
C(G)	control group
ccTGA	congenitally corrected transposition of the great arteries
CHD	congenital heart disease
CHD-TAAQOL	CHD-TNO/AZL adult quality of life.
cIMT	carotid intima media thickness
CMRI	cardiac magnetic resonance imaging
CoA	coarctation of the aorta
CPET	cardiopulmonary exercise test
CSAPPA	Childrens's Self-Perception of Adequacy and Predilection of Physical Activity Scale
cSBP	central systolic blood pressure
DT	dyspnea threshold
EBS	Ebstein's anomaly
HLHS	hypoplastic left heart syndrome
HR	heart rate
HRPF	health-related physical fitness
HRQoL	health-related quality of life
I(G)	intervention group
IMT	Intima-media thickness
IOM	American Institute of Medicine
Mesh terms	Medical Subject Headings
METS	metabolic equivalents
MVC	maximum voluntary contraction
MVPA	Moderate to vigorous physical activity
N/A	not applicable
NIRS	near-infrared spectroscopy
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
PA	physical activity

PAQ	physical activity (self-efficacy) questionnaire
PDA	patent ductus arteriosus
PDMS-2	Peabody Developmental Motor Scale-version 2
PEDro	Physiotherapy Evidence Database
PF	Physical Fitness
PFO	patent foramen ovale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	pulmonary valvular stenosis
PSPP - scf	Physical Self-Perception Profile - short clinical form
PubMed	Public/Publisher MEDLINE
pVO2	peak oxygen uptake
PWV	pulse wave velocity
QoL	Quality of life
RCT	randomized control trial
RV	right ventricle
Sars-Cov-2	Severe Acute Respiratory Syndrome Coronavirus 2
SF-36	Short Form 36 health survey
SWLS	satisfaction with life scale
TAC	truncus arteriosus communis
TAPVC	total anomalous pulmonary venous connection
TCPC	total cavopulmonary connection
TGA	Transposition of the great arteries
THR	training heart rate
ToF	Tetralogy of Fallot
UVH	univentricular heart
VE	minute ventilation
VSD	ventricular septal defect
VT	ventilator threshold
WHO	World Health Organization

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1 Introduction

1.1 General Introduction

Every year about one percent of all live births worldwide are with a congenital heart disease (CHD).[1-3] Representing 28% of all congenital malformations, CHD is thereby the most prevalent major congenital abnormality of individual organs in humans.[4,5] Very broadly, CHDs are structural anomalies of the heart or the great vessels of potential or actual functional importance.[6] A variety of symptoms and pathomechanisms go along with these malformations, some of which require early intervention soon after birth. Over the last seven decades, the life expectancy of patients with CHD has improved substantially.[7,8] Today almost 90% of all patients with CHD can expect to reach adulthood [4,9-11] so simply ensuring survival is not the main concern of medical aftercare anymore.

Neurological deficits in the unborn child with CHD can already develop in utero and carry over into adulthood, where they can also impair motor development.[12] These impairments can affect the psychosocial development of a child with CHD and have a lifelong impact on their daily life.[13,14] As a result, psychosocial aspects such as health-related quality of life (HRQoL) were increasingly addressed and integrated into the clinical care of these patients.[15-17]

Additionally, activity restrictions by healthcare professionals or parents can further contribute to motor deficits. In the absence of important movement experiences, reduced health-related physical fitness (HRPF) can manifest as well.[18,19] Promoting physical activity (PA) and exercise are recommended for all patients with CHD [17,20-22] as these target group bear a higher risk for cardiovascular disease.[23,24] Sufficient sensitization and guidance of the parents and the early support of their children could counteract this development.

Since the very first exercise intervention for children with CHD in 1981 [25] specialized centers usually offered programs that were supervised both personally and through appropriate monitoring instruments.[26] Supervised programs requiring the patients to be on site. Consequently, such program offerings can mainly be used by patients who live close to a study center. Modern monitoring instruments use digital technologies like wearables or smartphones, which are becoming more and more part of the health care sector in general.[27,28] Such use of modern information and communication technologies to improve health care is generally summarized in the term eHealth.[29] Possible advantages of eHealth become particularly evident in the current highly infectious Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-Cov-2) pandemic.[30,31]

Bridging the gap for patients at distance, home-based exercise interventions can be safe, feasible, and useful in the cardiac rehabilitation of patients with CHD.[32] Nevertheless, the number of digitally supported and delivered home-based interventions for this target group is quite low.

This dissertation provides the first comprehensive evaluation of a web-based exercise intervention for children and adolescents with moderate or complex CHD.

1.2 Medical Background

During embryonic development, a complex sequence of different steps creates all organs including the heart within the first 42 days. Around the 22nd day of pregnancy, the first rhythmical contractions of a muscle layer surrounding a large blood tube become visible which further on develop into the heart (**Figure 1a**). The organogenesis of the heart follows fixed steps. If there are deviations from these steps, malformations develop, which results in CHD.[33]

Heart defects can occur isolated or in a combination of multiple defects. Each type of defect can have a different effect on oxygen saturation. The resulting level of oxygen saturation leads to a distinction in cyanotic and acyanotic heart defects. Depending on the severity of the heart defect, however, CHD can also be differentiated into simple, moderate, and complex lesions.[34] The prevalence of CHD in Germany is 107.6 per 10.000 live births with 60.4% simple, 27.4% moderate, and 12.0% complex defects.[5] In each of the three severity classes, different underlying heart defects are requiring different levels of medical care.

The exercise capacity of a patient with CHD does not necessarily reflect the classified severity of the heart defect. This means that patients with moderate or even complex heart defects can be able to exercise almost normally. However, patients with all degrees of severity and especially with complex CHD have a higher risk of premature mortality compared to the normal population.[35] The majority of these are due to the heart defect itself or resulting cardiovascular risk factors.[36] Additionally, these patients struggle with motor impairments. Therefore, interventions become even more obviously necessary.[18,19,37,38]

In the context of this dissertation, two studies were conducted investigating the use of training interventions in patients with CHD. One of them investigated a web-based exercise intervention for patients with moderate and complex CHD. For this reason, heart defects are briefly explained in the following section, especially for participants of this intervention.

Pulmonary valvular stenosis

The pulmonary valvular stenosis (PS) with right-sided obstruction (6.1 of 10.000 live births in Germany) [5] can be at sub-, valvular, and supravalvular level or in the periphery of the pulmonary arteries (**Figure 1b**). By narrowing the pulmonary flow, the deoxygenated blood is restricted from entering the lungs which is why the pressure in the right ventricle increases resulting in right ventricular hypertrophy.[33 39]

Aortic valve stenosis

With 2.2 of 10.000 live births in Germany [5] the aortic valve stenosis (AS) characterizes an obstruction at the sub-, valvular, and supravalvular level (**Figure 1c**). This can lead to a restriction of the blood flow between the left ventricle and the aortic arch. This creates permanent resistance against which the left ventricle has to work and consequently results in hypertrophy.[33,39]

Coarctation of the aorta

The coarctation of the aorta (CoA) is a constriction in the aorta between the outlet of the left subclavian artery (3.9 of 10.000 live births in Germany) [5] and the aortal orifice of the ductus arteriosus botalli (**Figure 1d**). The consequences of narrowing depend on its proximity to the duct and whether there are collateral blood vessels. Typically, there is a difference in blood pressure between the upper and lower half of the body. Further, a hypertrophy of the left ventricle occurs due to the increased work required to sufficiently perfuse the peripheral segments.[33,39]

Ebstein's anomaly

Ebstein's anomaly (EBS) is characterized by one or more malformations of the tricuspid valve (**Figure 1e**). In addition, the sails of the valves are displaced apically, which divides the right side of the heart into a right atrium, an atrialized, and a residual ventricle. Both the pathological malformations and the valve attachment can be the cause of insufficiency. Due to the highly variable manifestation of pathological-anatomical changes (0.4 of 10.000 live births in Germany), [5] the clinical picture of EBS is very diverse.[33,39]

Tetralogy of Fallot

The Tetralogy of Fallot (ToF) is a combination of four different heart defects (**Figure 1f**). These include a ventricular septal defect, an obstruction of the right ventricular outflow tract, an "overriding" aorta, and right ventricular hypertrophy (2.6 of 10.000 live births in Germany). [5] Since the ventricular septal defect and the right ventricular outflow tract obstruction is pathophysiological the most important, these two components determine the necessary surgical strategy.[33,39]

Transposition of the great arteries

The transposition of the great arteries (TGA) is characterized by both ventricles and atria in normal relation to each other (2.3 of 10.000 live births in Germany). [5] However, the aorta emerges from the morphologically right ventricle, while the pulmonary artery emerges from the morphologically left ventricle (**Figure 1g**). A newborn can only survive if there is some connection between the right and left hemispheres of the heart (patent ductus arteriosus, patent foramen ovale, or ventricular septal defect).[33,39]

Single ventricle defects

This group (3.3 of 10.000 live births in Germany) [5] includes all those heart defects in which the left chamber is underdeveloped and therefore too small such as hypoplastic left heart syndrome (**Figure 1h**) or a valve is missing (pulmonary atresia, tricuspid atresia). These heart defects are treated palliative in several surgical steps, to create two separate blood circuits. The last step includes a total cavopulmonary connection (TCPC), which creates a so-called "Fontan circulation". In this case, the blood flows passively through the pulmonary circulation without any active support of the heart.

Miscellaneous

This category is a summary of heart defects that show such a low prevalence in their appearance, which is why they are classified together (3.3 of 10.000 live births).[5] This includes the truncus arteriosus communis (TAC) with 0.5 of 10.000 live births in Germany.[5,33,39] The TAC is a combination of an intracardiac defect in the ventricular septum and a fusion of the pulmonary artery with the aorta (**Figure 1i**).[37,38]
Another rare defect (0.4 of 10.000 live births in Germany) [5] is the congenitally corrected transposition of the great arteries (ccTGA). While on the atrial level everything is morphologically correct, both ventricles are inverted and additionally, the great arteries are connected inverse (**Figure 1j**). The normal circulatory blood flow is maintained. However, both a morphologically unfavorable ventricle and a tricuspid valve of low capacity suffer from the high pressure against which they have to pump. In addition, the excitation conduction system of the heart is abnormal.[33,39]

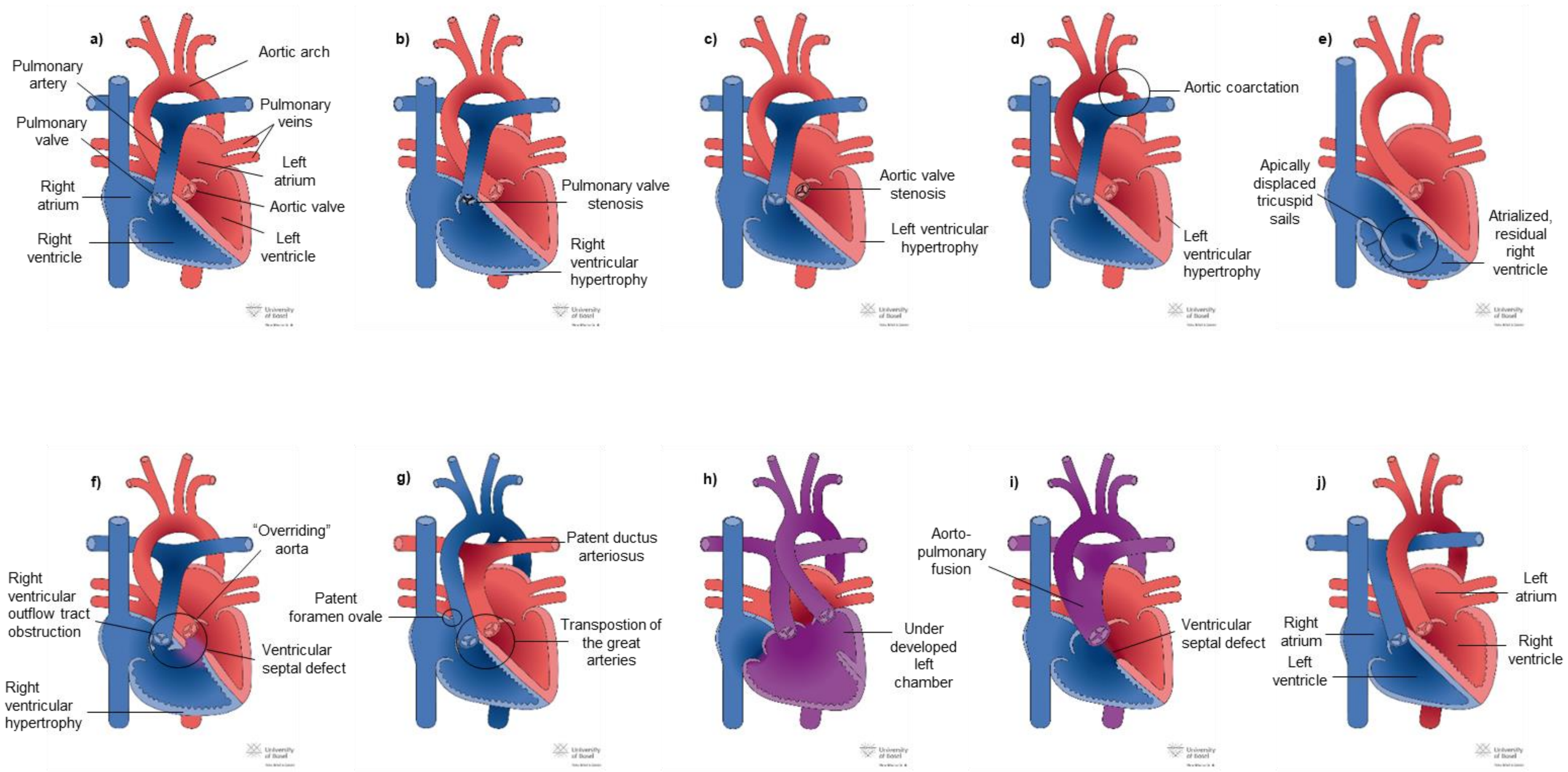

Figure 1 Congenital heart defects.
a: Healthy heart; **b**: Pulmonary valvular stenosis, **c**: Aortic valve stenosis; **d**: Coarctation of the aorta; **e**: Ebstein's anomaly, **f**: Tetralogy of Fallot, **g**: Transposition of the great arteries; **h**: Hypoplastic left heart syndrome; **i**: Truncus arteriosus communis; **j**: Congenitally corrected transposition of the great arteries. All illustrations are modified from http://www.chd-diagrams.com [40]

1.3 Web-based exercise Interventions

With the beginning of the first developments of computers in the late 1940s, rapid technical progress arose. Together with the invention of the “World Wide Web” [41] and in particular its free availability, the new technologies paved the way for the beginning of the “digital revolution”. From then on, the performance of computers and therefore digital technologies developed even more radically within a few decades and expand into almost all areas of society around the world. The World Wide Web, since the mid 90’s officially called the “Internet” simplified access to information on remote servers. Going along was for the first time free access to human knowledge. Due to its interconnectivity, the cultural importance of the internet is comparable to the invention of letterpress printing.[42] Since the second generation of the Web (Web 2.0),[43] users have been further able to share their own content like text, audio, or video files and interact with each other on social platforms, connecting people worldwide even more closely.[44]

In 2010, the number of networked computers exceeded the number of people living at that moment for the first time in history. The driving force behind digitalization continues to act at the macro and micro levels of society, where it has also spread to social sub-sectors such as education, research, administration, health care, or sports. New developments such as Nintendo Wii™ or, more recently, Pokémon Go™ show that modern technological and digital approaches can be useful in initiating PA [45] as well as in the rehabilitation of patients.[46]

At the same time digitalization has also had an impact on the health sector, where the terms "eHealth", "telemedicine" and "mHealth" emerged. While telemedicine refers to

> “*the use of medical information exchanged from one site to another via electronic communications to improve a patient’s clinical health status*”,[47]

mHealth describes both the practice of medicine and public health with support from mobile devices for health services and information.[48]

Nevertheless, each of them was initially used interchangeably to describe almost everything in the context of computers and medicine, that would improve general health and the health care system.[49] Nowadays, there are various definitions for eHealth [50] and the term encompasses both telemedicine and mHealth.[51]

According to the most accepted and frequently cited definition

> “*eHealth is 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. In a broader sense, the term characterizes not only a technical development, but also a state-of-mind, a way of thinking, an attitude, and a commitment for networked, global thinking, to improve healthcare locally, regionally, and worldwide by using information and communication technology*.” [29]

Consequently, eHealth is more than just a simple combination of the internet or any other technical term associated with electronics and medicine, but rather the chance to change the interrelation between health professionals and patients. The “e” is more suitable for efficiency, enhancing quality, evidence-based, empowerment, encouragement, education, enabling, extending, ethics, and equity.[29] More specifically, for the health system, eHealth means empowering consumers and patients, promoting partnerships between patients and providers to increase patient engagement and achieve patient-centered health care.[52] For this purpose, mHealth applications became more relevant in health professions [53] to deliver information such as patients' vital signs monitored in real-time, to practitioners, researchers, and, if necessary, treatment can be provided directly via mobile telemedicine.[54] This can have beneficial effects on overall mortality, hospital stays, and the number of hospital admissions of patients with heart failure.[55]

Especially in the current ongoing pandemic of SARS-Cov-2, eHealth solutions can support the basic care of chronically ill patients, e.g. virtual visits,[56] disseminate novel coronavirus related information to medical staff[57] or even identify cases and trace contacts.[58] But also, in the long run, eHealth interventions can effectively contribute to healthy aging [59] in terms of health promotion. An important contributor to healthy aging is regular PA, which can be easily and effectively promoted through web-based interventions.[60] At the same time, web-based exercise interventions can provide home-based rehabilitation for adult [61,62] and pediatric [63] patients with chronic diseases. Although exercise interventions performed in a home-based setting are feasible and safe for children with CHD,[32] the possibilities of web-based cardiac rehabilitation are still widely underutilized. There are a few eHealth interventions for patients with CHD. To date, just one study focused on encouragement for PA among adolescent patients after repaired complex CHD.[64] The rest are predominantly focusing on primary aftercare such as home-monitoring.[65]

1.4 Health-Related Physical Fitness

During World War II and in the post war time, youth fitness tests primarily focused on physical fitness the “ability to sustain long, hard, muscular effort” [66] and therefore mainly examined performance-related fitness, also known as a person’s ability to carry out a certain physical task or activity. In the following years, an elevated prevalence of overweight and obesity among American adolescents further expanded the scientific interest in the effects of fitness on health. To better understand the fitness status among contemporary children and adolescents, scientific motivation continued to develop a youth fitness test that primarily focused on health-related fitness. The “Texas Physical Fitness Motor Ability Test” [67] can be dated back to the late ’70s and was one of the first test batteries including health-based test items.[68]

However, there was still a lack of a standardized testing system at a national level, taking into account the relationship between physical fitness and functional health and not exercise performance. Therefore, the first national health-related physical fitness (HRPF) test was introduced, measuring it within one test battery.[69]

HRPF can be defined as:

> *“a state of being that reflects a person’s ability to perform specific forms of physical activity/exercise or functions and is related to present and future health outcomes.”* [70]

It includes Physical Fitness (PF) which is “a set of attributes that people have or achieve, that relates to the ability to perform physical activity”.[71] Therefore, it is comparable to a biological or physical characteristic that comprises health-related and skill- or performance-related fitness.[70]

PA, on the other hand, describes a behavior, that is defined as "any bodily movement produced by skeletal muscles that result in energy expenditure".[72] PA in the sense of health-enhancing energy expenditure includes any activities of large muscles, even with light intensity.[70] Both physical fitness and activity are in a reciprocal relationship with health and with each other. Furthermore, there are controllable factors, such as lifestyle or personal characteristics, and uncontrollable factors, such as heredity or environment, which influence this relationship.[73]

Health-related physical fitness is based on a multidimensional construct. Its framework has been continuously developed.[72,73] The following section briefly explains its most important aspects defined by the American Institute of Medicine (IOM).[68]

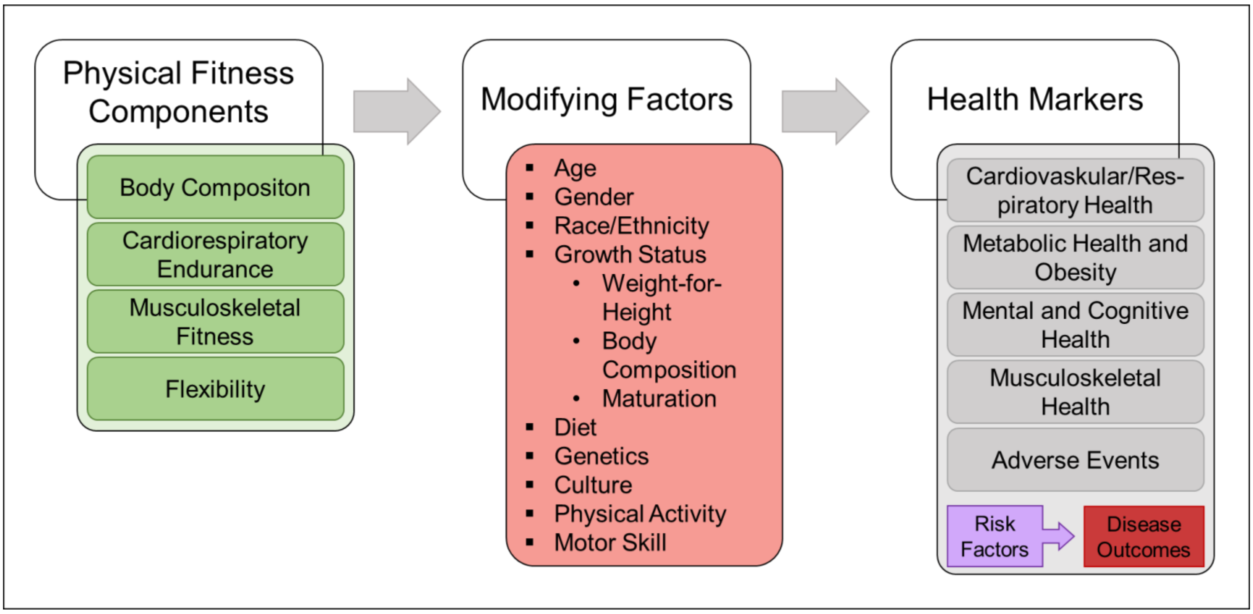

Figure 2 Framework of Health-related physical fitness modified from the IOM.[68]

In this framework are four major components of physical fitness (**Figure 2**). The component Body Composition accumulates body weight, fat, muscle, and bone content. Cardiorespiratory endurance means the capacity to execute whole-body exercises at medium to high-intensity levels over a long time.[68] The third component contains the Musculoskeletal Fitness, which can be further subdivided into:

- Muscle Strength:

  "The ability of a single muscle or group of muscles to produce force, torque or movement about a single or multiple joints, typically during a single maximal voluntary contraction and under a defined set of controlled conditions, which include specificity of movement pattern, muscle contraction type (concentric, isometric, or eccentric), and contraction velocity." [68]

- Muscle Endurance:

  "*The ability of a muscle or group of muscles to perform repeated contractions against a constant external load for an extended period of time. The constant load can be either an* *absolute external resistance, which provides a measure of absolute endurance, or a relative load based on an individual's maximal strength, which provides a measure of relative endurance."* [68]

- Muscle Power:

"A physiological construct reflecting the rate at which work is performed." [68]

A fourth component of the HRPF Framework Flexibility describes

"The ability to move the joints through a range of motion. Flexibility reflects the intrinsic property of body tissues (e.g., muscles, tendons, bones) that determines the range of motion achievable without injury at a joint or group of joints". [68]

Each of these four components is associated with health markers, which can be influenced by modifying factors such as age, gender, and further aspects. On the other hand, these modifying factors can independently affect an individual's level of fitness. The term Health Marker describes the relationship between risk factors and disease outcomes, which could be mainly studied within adults, who may develop diseases and conditions, such as a heart attack, that are usually not possible in this way in childhood.[68]
The FitnessGram® [74] is an official national fitness test battery in the United States since 1994 and reflects the essential cornerstones of the HRPF framework of the IOM.[68] It distinguishes between three components of health-related fitness, as it dispenses with muscle power and considers mobility as part of musculoskeletal fitness.[70] In addition, the FitnessGram® assesses functional fitness, which reflects the ability to effectively pursue the usual activities of daily life, e.g. participating in leisure time activities without fatigue.[75]
It is a useful and interesting assessment tool for children and adolescents with CHD who often show skill-based limitations from early infancy.[76-78] Tracked into adulthood such limitations can have further negative effects on HRPF and muscle strength.[79-82] Moreover, even in adult patients with CHD, diseases of cardiovascular origin [83] are a health burden associated with reduced PA.[84] Children who are habitually physically active will also do so later as adults.[85] Its association with HRQoL further emphasizes the need for PA promotion and making early testing of HRPF even more important.[86]

1.5 Health-Related Quality of Life

Quality of life (QoL) reaches far back into ancient times when Aristoteles and other philosophers already critically studied the concept. Since then, both philosophers and social scientists have continued to interpret and apply this term in different ways in the context of current political and social issues. An important development in QoL research was the expansion of the concept of health by the World Health Organization (WHO). Health accordingly encompasses physical, mental, and social well-being and is more than the absence of illness.[87] In addition, the interest in patient care has expanded to include whether the medical treatment that has taken place has also improved the patient's life.[88] Based on the principle of "adding life to years and not just years to life", more and more medical subfields consider morbidity, not as the main criterion in the evaluation of therapy anymore.[89]

With its definition of QoL [90], the WHO Quality of Life Group has set a milestone building an important conceptual basis for health-related quality of life (HRQoL). Although there is still no universal scientific definition of HRQoL, most attempts to grasp this concept contain two central aspects. On the one hand, HRQoL is a multidimensional construct that describes the physical (e.g. complaints), emotional (e.g. mood), mental (e.g. concentration), social (e.g. contacts), and everyday functional (e.g. work) aspects from a patient's and/or observer's perspective. On the other hand, it includes both an objective and subjective perspective in each domain.[91] The objective perspective reflects what an individual can do, which is important to define the degree of health, while the subjective perspective reflects the meaning of quality of life to the individual.[92] However, additional factors, such as an individual's character traits, e.g. personality, processing strategies, and structural features, e.g. living conditions and social class, can further modify HRQoL.[91]

The use of standardized questionnaires, which meet all psychometric requirements, allows all relevant subjective components to be recorded in different items and at the same time ensures their comparability based on an overall value or index. A distinction can be made between generic, chronic generic (disease-comparing), and targeted (disease-related) measuring instruments.[93] While generic instruments provide representative population-based data or serve to compare the quality of life of different diseases, chronic generic instruments focus in particular on the representation of experiences of chronic disease as a whole, independent of the individual diagnosis. The targeted instruments, on the other hand, reflect the specific challenges of the disease and treatment of those affected, and also include health economic measurement instruments for evaluating the costs and benefits of therapies.[94]

However, the use of such instruments in pediatrics has only been established since the early 2000s.[93] Besides the ability of a child to reliably reflect and assess the quality of life, it can also depend on its age and development status.[91] Nevertheless, today there is a variety of generic,[95-97] chronic generic [98] and also specific instruments [99] that meet the special requirements of pediatrics are used both nationally and internationally. The KINDL® [95] questionnaire is one of the pioneers among the generic instruments for the child's self-report and the parental external report which is also used for children with CHD.[100]

1.6 Measures of Arterial Stiffness

Arterial stiffness is a parameter representing the dynamic characteristics of the arteries, which depends on the structure and function of the vessels and the arterial pressure. These three components act independently and together to cause changes in arterial stiffness. Arterial pressure is the main determinant of arterial stiffness. Factors influencing arterial pressure, such as increased heart rate, stroke volume, vascular resistance, or early wave reflections can increase arterial stiffness. The three main groups of non-invasive methods for measuring arterial stiffness are the analysis of arterial pressure waveform, pulse wave velocity (PWV), and central systolic blood pressure (cSBP).[101] Both PWV and cSBP are “functional parameters” of the arterial stiffness. PWV was first described by Bramwell and Hill [102] and corresponds to the pressure pulse generated during ventricular ejection and then moves along the arterial system at a rate determined by the geometry and elastic components of the arterial wall.[101]

Over time, the techniques for analyzing and characterizing the arterial pulse evolved from simple assessment by palpation to more complex methods using technical devices.[103] There are mobile devices, such as the Mobil-O-Graph® (I.E.M GmbH, Stolberg, Germany) that combine cuff oscillometry and PWV analysis in a convenient way to measure oscillometric PWV during 24-hour ambulatory blood pressure monitoring.[104] An inbuilt algorithm of the device uses a transfer function to calculate PWV and cSBP based on the peripheral waveform.[105]

Arterial stiffness plays a significant role in the development of cardiovascular disease [101] and its association to physical activity have previously been outlined in adult and pediatric cohorts.[106,107] The Mobil-O-Graph® has shown good validity and applicability in several studies, even in patients with CHD.[108,109]

Starting in the early 1990s, high-resolution B-mode ultrasonography is nowadays established as one of the more powerful tools to evaluate subclinical atherosclerosis.[101] Pignoli and colleagues [110] were important pioneers in this respect. These found strong associations between histological findings and ultrasound examinations of the posterior wall of the intima-media thickness (IMT) in the common carotid artery.

As a measurement of the arterial IMT wall compound, the carotid intima-media thickness (cIMT) is a marker for structural changes (**Figure 3**). It can be reliably used as a surrogate for subclinical atherosclerosis as well as end point for best medical treatment.[111,112] Due to the superficial location of the common carotid artery at the neck, it is easily accessible for examination. cIMT is a convenient and non-invasive examination.[111,113] Therefore it is also widely used for clinical studies in either healthy children and adolescents or with chronic conditions such as type 1 diabetes mellitus or metabolic syndrome.[101] However, it can also be useful to assess cardiovascular risk factors in pediatric patients with CHD.[114] In particular children with repaired CoA or TGA tend to have increased cIMT compared to healthy children and thus an enhanced risk for early changes in vascular structure.[115,116] Both are examples of types of heart defects with moderate or complex severity and therefore interesting for the intervention. Further adult patients with CHD are at higher risk for cardiovascular mortality.[117-119] Subclinical signs of atherosclerosis can be already detected in childhood, which is why measurements of functional parameters (PWV, cSBP) and structural parameters (cIMT) of arterial stiffness are included in the study protocol. However, since it was a secondary outcome of the study protocol (Section 2.2.) it was not tied to this dissertation and therefore was mentioned here only for completeness.

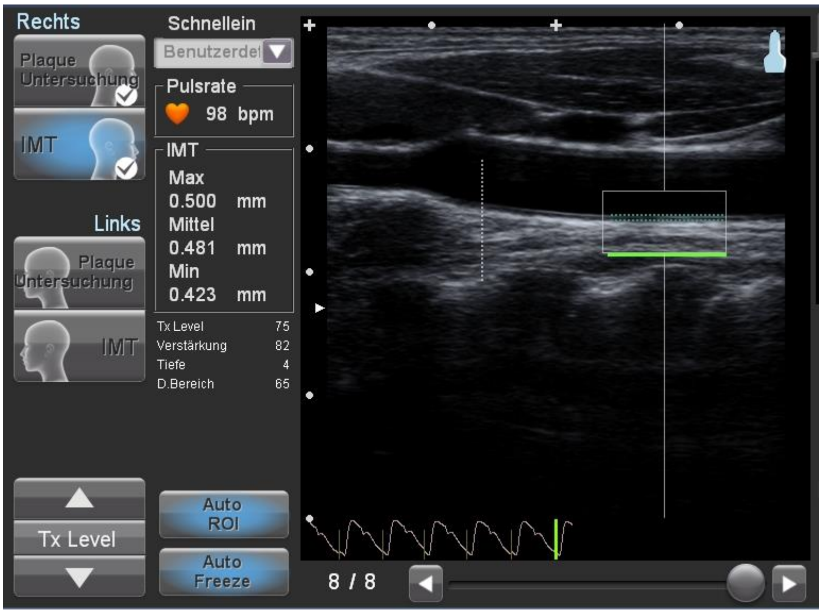

Figure 3 Ultrasound of the cIMT at common carotid artery (longitudinal).

1.7 Purposes of the Project

There were two main purposes of this dissertation:

- The primary goal was to improve health-related physical fitness in patients with CHD using a 24-week web-based exercise intervention and monitor their compliance and adherence with the training.
- The secondary purpose focused on enhancing psychological issues such as HrQoL resulting from the 24-week web-based exercise intervention.

For this reason, three scientific studies were published in fulfillment of this dissertation:

Study I: *Current state of home-based exercise interventions in patients with congenital heart disease: a systematic review*

(1) To evaluate literature and identify the potential beneficial effects of a home-based exercise intervention for patients with CHD.

Study II: *Web-Based Motor Intervention to Increase Health-Related Physical Fitness in Children with Congenital Heart Disease: A Study Protocol*

(1) To transparently disclose the study design, methods, and objectives in advance.

Study III: *E-health exercise intervention for pediatric patients with congenital heart disease: a randomized controlled trial*

(1) To investigate the effect of a 24-week web-based exercise intervention on HRPF and HRQoL in patients with moderate or complex CHD.
(2) To investigate patient's compliance and adherence with the 24-week web-based exercise intervention

2 Methodology

Two basic components have been addressed to improve the validity and reliability of the web-based exercise intervention (**Figure 4**).

For the greatest possible transparency of the planned intervention, all study intentions, including pre-registration in a clinical trial registry, were published before. A detailed overview of the key scientific questions, study design, content of the intervention, measurement outcomes as well as its registry in trial.gov is provided in subsection 2.2 of this chapter.

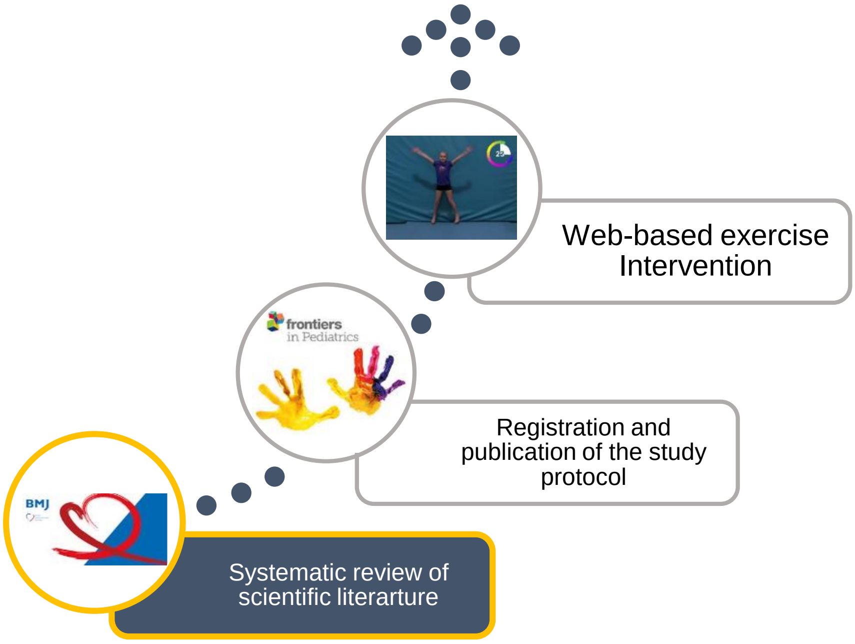

Figure 4 Preliminary methodological considerations.

The application of a web-based exercise intervention, specifically designed to improve motor skills in pediatric patients with CHD, is a completely novel approach. With this intervention format, a new, previously almost unused option of home-based rehabilitation should be opened up to this target group. Therefore, a systematic literature review was carried out first, which is described in section 2.1. This section provides a detailed overview of the feasibility and safety of such interventions and rather highlights the challenges of compliance and adherence to the interventions.

2.1 Current state of home-based exercise interventions in patients with congenital heart disease: a systematic review [32]

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Published in: **Heart** (DOI: http://dx.doi.org/10.1136/heartjnl-2019-315680)

Individual contribution:
The PhD candidate is the principal author of this paper. He designed the systematic search, performed it on all databases, and drafted the manuscript. In cooperation with the Co-authors, he further screened and assessed the search results. PD Dr. Jan Müller revised the manuscript and Prof. Dr. Alfred Hager, Prof. Dr. Renate Oberhoffer-Fritz, and Prof. Dr. Peter Ewert did the final proof of the manuscript. The PhD candidate and PD Dr. Jan Müller processed the submission procedure until publication.

Abstract

Objective: Home-based exercise training is a promising alternative to conventional supervised training for patients with congenital heart disease (CHD). Even though the beneficial effect of exercise interventions is well established in patients with CHD, knowledge concerning the variety and utility of existing programs is still lacking.

Therefore, the aim of this review is to give an overview of existing home-based exercise interventions in patients with CHD.

Methods: A systematic search was performed in PubMed, Cochrane, Scopus, and PEDro (2008–2018) for relevant clinical trials that provided any kind of home-based exercise with patients with CHD. All articles were identified and assessed by two independent reviewers. Seven articles with 346 pediatric CHD (18 months to 16 years) and five articles with 200 adults with CHD (21–41 years) were included.

Results: Most studies performed a supervised home-based exercise intervention with children and adolescents exercising at least three times per week with a duration of 45 min for 12 weeks. Reported outcome measurements were health-related quality of life and physical activity, but mostly exercise capacity measured as peak oxygen uptake that improved in four studies (1.2%, 7%, 7.7%, 15%; $p<0.05$), walking distance in two (3.5%, 19.5%, $p<0.05$,) or walking time (2 min, $p=0.003$) in one. The dropout rates were high (15%), and compliance with the training program was not reported in the majority of the studies (58%).

Conclusions: Home-based exercise interventions are a safe, feasible, and useful alternative to supervised cardiac rehabilitation for all age groups of patients with CHD. Nevertheless, training compliance represents a major challenge.

What is already known about this subject?

Exercise interventions or cardiac rehabilitation are well established as part of the treatment of especially adult patients with congenital heart disease (CHD). Several exercise-training programs in this patient population have shown that these methods are safe, feasible, and improve functional outcome measures. Most of the studies are hospital-based and supervised and even when interventions were home-based, exercise was not carried out alone and independently, but was supervised by a control authority.

What does this study add?

Exercise interventions in the pediatric population are still underutilized and the optimal structure and efficacy of such programs are unclear. Aside from feasibility and safety, this systematic review aimed to give an overview of existing home-based exercise interventions for patients with CHD and identify potential beneficial effects. To our knowledge, this is the first study focusing on home-based exercise interventions beginning from very early infant to adult patients with CHD.

How might this impact on clinical practice?

Our findings outline that in general, home-based exercise interventions are feasible, safe and a useful alternative to supervised cardiac rehabilitation for all age groups of patients with CHD. Despite the low prevalence of central outpatient CHD rehabilitation, the promotion of rehabilitation programs might be done in shifting the intervention to the patient’s home. Adherence and compliance are lacking in most studies and need to be addressed further.

Introduction

Exercise interventions or cardiac rehabilitation are commonly recommended, well-established non-pharmacological treatment of different cardiac conditions,[120-123] particularly in patients with congenital heart disease (CHD).[20,124,125] Typically these patients suffer from impaired exercise capacity,[126] restrictive lung physiology,[127] impaired physical activity (PA) [128] or reduced health-related quality of life (HRQoL).[129,130] Several exercise-training programs in this patient population have already shown that these methods are safe, feasible, and improve functional outcome measures.[26,131,132]

While the literature is diverse in adult congenital heart disease (ACHD), exercise interventions in the pediatric with CHD are still underutilized and optimal structure and efficacy unclear. Even though the number of studies has increased in recent years, almost all of the studies are hospital-based and supervised.[131] And even when interventions were home-based, exercise was not carried out alone and independently, but supervised by a control authority.[26,131,132]

Therefore, it is not surprising that supervised interventions within these settings were successful. On the one hand, shifting the responsibility of the intervention to the patient is the real challenge as central outpatient rehabilitation for patients with CHD is rarely offered due to the relatively low prevalence of CHD.[131,133] On the other hand, a non-supervised exercise in form of a home-based training program allows for customization of time, location, and exercise partner. Unfortunately, such flexibility may come at the cost of compliance and adherence to the program in general.[120]

Even if home-based exercise interventions are feasible information on whether CHD patients can benefit from such interventions is limited. Therefore, this systematic review aimed to give an overview of existing home-based exercise interventions for patients with CHD and identify potential beneficial effects.

Methods

Search Strategy

A systematic literature research was carried out in the electronic databases PubMed, Cochrane, Scopus, and PEDro that referred to January 2008 until December 2018. Relevant clinical trials, randomized controlled trials, or reviews in English language were identified by two independent reviewers. A standard protocol with search terms was generated according to the PICO-C Method [134] and connected in the following combination:

1. congenital heart disease OR congenital heart diseases OR congenital heart defect OR congenital heart defects AND
2. exercise OR exercise training OR exercise program OR physical activity OR physical exercise OR physical training OR home-based OR supervised OR web-based.

Mesh terms (Medical Subject Headings) and similar filters (clinical trial, randomized controlled trial, review, systematic reviews, published in the last 10 years, Humans, Child: birth-18 years, Adult: 18+ years) were used if available and if necessary, adapted in an appropriate way. According to the latest PRISMA statement for systematic reviews and meta-analysis,[135] supplementary reference lists were analyzed to detect further eligible articles.

Data collection

Both reviewers screened all relevant articles for title and abstract which had to fulfill the basic inclusion criteria: history of CHD as well as any kind of un-/supervised exercise intervention in a home-based setting. At least one of the two reviewers had to consider a reference eligible, a third reviewer was consulted to dissolve disagreement before the full text was obtained for a complete assessment.

To quantify the quality of the included literature both reviewers used the PEDro Scale [136] scoring the articles on an 11 item Delphi list.[137] Additionally, methodological assessment via the PEDro Scale was used. Generally, the PEDro Scale ranges on a 0-11 Item list. However, the first item (criteria of eligibility) obtains external validity which in general is not used to calculate the total score.[136] The quality assessment of five studies [138-142] was adopted from the PEDro Review group, the others were rated by the two independent reviewers. Standardized extraction form customized to the Cochrane Collaboration’s model for data extraction [143] was applied. (Detailed scheme see online supplement).

Results

Description of selected studies

The initial search provided 553 potential abstracts. After removing duplicates 468 articles remained. Further screening of title and abstract led to 37 potentially relevant articles and were retrieved for full-text analysis. Overall, 12 articles [138-142,144-150] with a total of 346 pediatric CHD (18 months to 16 years), and 200 ACHD (21 - 41 years) met all inclusion criteria (**Figure 5**). Median PEDro Score of the 12 articles was five and ranged from two to eight (**Table 1**).

Study characteristics

The majority of the included studies [138,139,144,146-148] performed home-based exercise interventions with pediatric CHD (8 to 16 years). One study used a play based parental led intervention with toddlers (mean age18 months),[149] the remaining focused on ACHD.[140-142,145,150] Four articles had different intervention groups,[145,147-149] the rest had an intervention and control group design, with [144,146] or without healthy controls.[138-142,150] All studies recruited their subjects in an outpatient setting with various CHD diagnosis (**Table 2**).

Determination of exercise program

Initial CPET provided individual heart rate at the anaerobic ventilatory threshold for pediatric CHD [138,144,146] and ACHD.[140-142,150] Additionally the BORG Scale was used to either instruct ACHD to achieve perceived exertion [140] or to generate an individual dyspnea threshold for exercise at home. Furthermore, previously measured activity level contributed to give an activity amount recommendation for pediatric CHD.[145] Motivational interviewing techniques to stimulate and maintain behavior change and increase activity suitable to CHD diagnosis,[139] physical activity behavior, healthy-lifestyle information and psychosocial support [148] helped to individualize pediatric CHD's intervention. Stieber and colleagues,[149] examining toddlers with CHD, used individualized child's developmental age-adapted play-based activities. One study [147] did not further elaborate on the in-person formalization of the exercise session.

Characteristics of home-based interventions

Five studies used a cycle ergometer or treadmill for pediatric CHD [138,144] or ACHD.[140,141,150] Programs for ACHD used step-aerobics [142] or gentle walking on flat.[145] Studies with pediatric CHD used running/swimming,[146] physical active play,[148] dynamic and static exercise [147] or play-based activities for toddlers [149] for their interventions. One study [139] did not clearly state the type of intervention (**Table 3**).

ACHD exercised six [150] to 24 weeks,[141] pediatric CHD eight [144] to 24 weeks.[139] One ACHD intervention started with six weeks of supervised training continuing with further six weeks of independent home-based training.[150]

Pediatric CHD performed a minimum of two [146] up to daily sessions [149] per week, the latter as a play-based activity with toddlers. ACHD's frequency ranged from one [150] to five [145] sessions per week.

Adult's sessions ranged from five [145] to 150 minutes,[141] children's sessions from 10 [149] to 45 minutes.[138,144,146-148] Interval training, exclusively conducted with ACHD, combined at least four minutes exercise and three minutes active recovery [142] up to ten minutes exercise and five minutes of active recovery,[138] exercising at 60% to 90% of individual maximum heart rate. ACHD incremented the number of intervals within the intervention time.[142]

Main outcomes of included studies

Detailed information on functional outcomes is presented in **Table 4**.

Exercise capacity (pVO_2)

PVO_2 of pediatric CHD was derived from CPET,[138,144,146,148] treadmill test [139] or estimated with 20-meter shuttle run test.[147] ACHD studies used CPET [140-142,150] or treadmill test.[145] Pediatric CHD improved pVO_2 (1.2%; p=.001),[147] walking distance (3.5%; p<.05) [146] or time (p=.003) [147] significantly. Dyspnea threshold and anaerobic ventilatory threshold were significantly associated (r=0.90; p<.001) for pediatric CHD.[144] ACHD improved pVO_2 (7%, 7.7%, 15%; p<.05) [140-142], walking distance (19.5%; p=.001) [150] or time (2 min, p=.003) [145] significantly.

Physical Activity (PA)

Objective PA in pediatric CHD [139,148] and ACHD,[145] subjective PA of pediatric CHD [139,146,148] and ACHD [140] and self-reported exercise for either pediatric CHD [146,147] or ACHD [140-142,145] were investigated. Objective PA level of ACHD [145] and pediatric CHD [139] increased significantly following exercise intervention and the number of adolescents reaching recommended 60 moderate to vigorous PA doubled after the intervention.[139] Nevertheless only 23% of ACHD with NYHA I, 15.8% of NYHA II, and none of NYHA III accomplished at least 30 minutes of MVPA on five or more days of the week at baseline.[145] Further subjective daily amount of PA time of pediatric CHD increased during the intervention but decreased to baseline level long term.[146]

Health-Related Quality of Life (HRQoL)

While ACHD's HRQoL remained unchanged before and after the intervention,[140-142] pediatric CHD [146] and ACHD [145] improved significantly reduced HRQoL baseline level after the 12-week intervention. Children's self-perceived HRQoL did not improve, but the parent's proxy perception of children's HRQoL improved significantly.[147]

Monitoring of Adherence and Compliance

Objective monitoring such as heart rate,[138,140,141,144] steps, and distance [147] and activity diaries [141,145,147] was used for ACHD and pediatric CHD.

To monitor ACHD's [140,141,145,150] and pediatric CHD's [139,147-149] adherence and promote compliance once a month up to weekly phone calls took place. The remaining studies did either not contact their subjects,[144,146] had an instructor-led setting [146] or weekly e-mail reminders combined with phone-calls.[142]

Median drop-out rate was 14.8% (7.1%-29.4%), one study with ACHD [138] did not report while pediatric CHD [144,149,150] had no drop-out. Overall training participation of pediatric CHD [147,149] and ACHD [140,141] varied from 50-100%, only 65% of pediatric CHD commented on adherence questionnaire.[148]

Potential harms

One ACHD discontinued exercise training due to feeling discomfort and possible arrhythmia during the exercise session.[140]

Nausea at baseline exercise test, ventricular bigeminy during the recovery phase, and calf injury during exercise were reasons not to include ACHD or pause the exercise intervention for a while.[142] Neither ACHD [141,145,150] nor pediatric CHD [138,139,144,146-149] had adverse events.

Discussion

This review outlined that exercise interventions for CHD patients executed in a home-based setting are feasible, safe, and improved functional outcomes. However, compliance and adherence are still major challenges as only a low number of studies report on these items. Regular exercise programs for CHD patients are often located close to specialized centers and people from remote areas need to overcome logistical challenges. Therefore, individualized exercise interventions executable in a home-based setting provide a useful alternative to bridge the gap for patients at distance.

In the past ten years, a relatively low number of 12 studies investigated any kind of home-based intervention and the median PEDro score of five illustrates a generally low-quality level. Two studies [145,147] with the lowest PEDro scores were controlled clinical trials not fulfilling the randomization process and blinding aspects. One study [145] matched their ACHD according to NYHA Class I-IV, whereas the other [147] was performed as a pilot-study only examining young Fontan patients. None of the remaining 12 studies accomplished PEDro criteria six (blinded therapists) which is not surprising, as a home-based intervention needs supervision for safety aspects and further motivational support.

Functional outcomes in pediatric CHD

Regular exercise usually can improve exercise capacity [147] and peripheral muscular function by enhancing strength and endurance.[138] Nevertheless co-morbidities can substantially impact exercise capacity.[144]

PA improved significantly [139,148] in the short-term while reaching weekly recommendations of PA declined in pediatric CHD [144] with higher NYHA class. Furthermore, changes of PA in adolescent patients with Fontan circulation were hardly maintained long term.[146] Pediatric CHD patients have lower levels of daily PA [151] and therefore healthcare providers should provide - similar to dietary or therapy advice - information and promotion of PA.[152] CHD has a considerable impact on the intensity of PA in adolescent patients, no matter if they do know about additional health effects of PA.[153] Further uncertainties of PA restrictions for pediatric CHD are possible triggers for parental overprotection, which is associated with heart-focused anxiety in later life.[154] Learning about personal physical limits and self-perceived functional capacity are important experiences in everyone’s life which is where the need for individually tailored PA recommendations for CHD patients emerges.

However, the current understanding of ‘health’ includes more than just physical aspects. HRQoL as a multidimensional concept of mental, social, and psychological well-being [100] was investigated in two studies.[146,147] Twelve weeks of endurance training improved significantly self-reported [146] and parent’s proxy perception of children’s HRQoL.[147] Parent’s proxy-report is a useful additive that can provide complementary information about their children’s HRQoL [155] even if there is a weak association between subjective physical capacity and objectively measured functional capacity.[151,156]

A training program is only as good as its adherence and compliance – a major challenge in all studies. Training participation in terms of adherence and compliance was only measured vaguely [147-149] or not at all.[138] Nevertheless four studies [139,147-149] mentioned regular phone calls to ensure patients' adherence and compliance. Traditional exercise programs for pediatric CHD are difficult to maintain, as these programs usually require considerable input of time, facilities, and resources. Highly motivated families and volunteers play a key role in good compliance and overall high participation rate in pediatric CHD interventions.[147,148]

Functional outcomes in adult CHD

Exercising continuously can improve the exercise capacity of ACHD.[140-142,145,150] Although there can be long symptomless time, long-term consequences or co-morbidities can affect exercise capacity, despite exercising regularly.[150]

Twelve weeks of gentle walking improved significantly short-term PA and HRQoL.[145]

In contrary HRQoL remained unchanged before or after the intervention.[140-142] ACHD have exceptionally good HRQoL,[140-142] which is hard to improve even further [157,158] or could have been biased by excluding symptomatic patients.[141] Therefore, it’s controversial whether CHD patients compensate for their condition well, have a high acceptance of their clinical situation or, on the contrary, denial of it.

Only two [140,141] studies measured training participation in terms of adherence and compliance while five [140-142,145,150] mentioned regular phone calls to ensure patients adherence and compliance. Even though overall training participation of 50% seems slightly low, this is in line with standard adult cardiac rehabilitation programs for patients with heart failure.[159] However, home-based exercise protocols still need to be combined with weekly phone calls to improve adherence and enhance compliance,[140] as ACHD still seem to be uncertain concerning safety and benefits of exercise.[141]

There are no clear recommendations concerning exercise interventions in pediatric CHD yet, but a duration of at least 12 weeks with two to three times per week, each session lasting at least 40 minutes, seems to be sufficient.[131] Another review recommends for young and adult patients with Fontan circulation a minimum total duration of eight weeks of exercise intervention at least two times per week.[160] This is in line with Duppen and colleagues,[26] who consider nine weeks of training supervised in person or by an adequate monitoring tool sufficient for pediatric CHD and ACHD. However, the previous study neither differentiated between home-based nor supervised performed exercise nor focused on specific CHD. In the end, both reviews postulated the need for more specific knowledge in terms of duration and intensity of individual training sessions and the whole exercise program. Aside from residual impairments, physiological changes can vary widely across different CHD types, which underlines the need for more individualized exercise programs for these patients.[131]

Limitations

Missing literature not published in the English language could have biased our results. So far, there are only a few interventions for children and adolescents with relatively low methodological quality. Additional RCT's raising statistical power could help to determine the future role of home-based exercise interventions in pediatric CHD after surgery. Moreover, future investigations should consider the psychological and educational influence on changing behavior in terms of implementing exercise in patient's everyday life.

Conclusion and Clinical Recommendation

Home-based exercise interventions are feasible, safe and a useful alternative to supervised cardiac rehabilitation for all age groups of CHD patients. Adherence and compliance are a major challenge in most studies and need to be addressed further. Age-appropriate behavior change concepts should be considered in the development of home-based programs for CHD patients. While pediatric CHD would be more likely to benefit from the involvement of family members, ACHD seems to need semi-supervised interventions to ensure adherence and compliance. Due to the low number of trials identified for the different life spans, specific recommendations concerning frequency and duration are still pending.

Acknowledgment

The study was supported by an unrestricted grant from the "Fördergemeinschaft Deutsche Kinderherzzentren e.V".

There are no conflicts of interest.

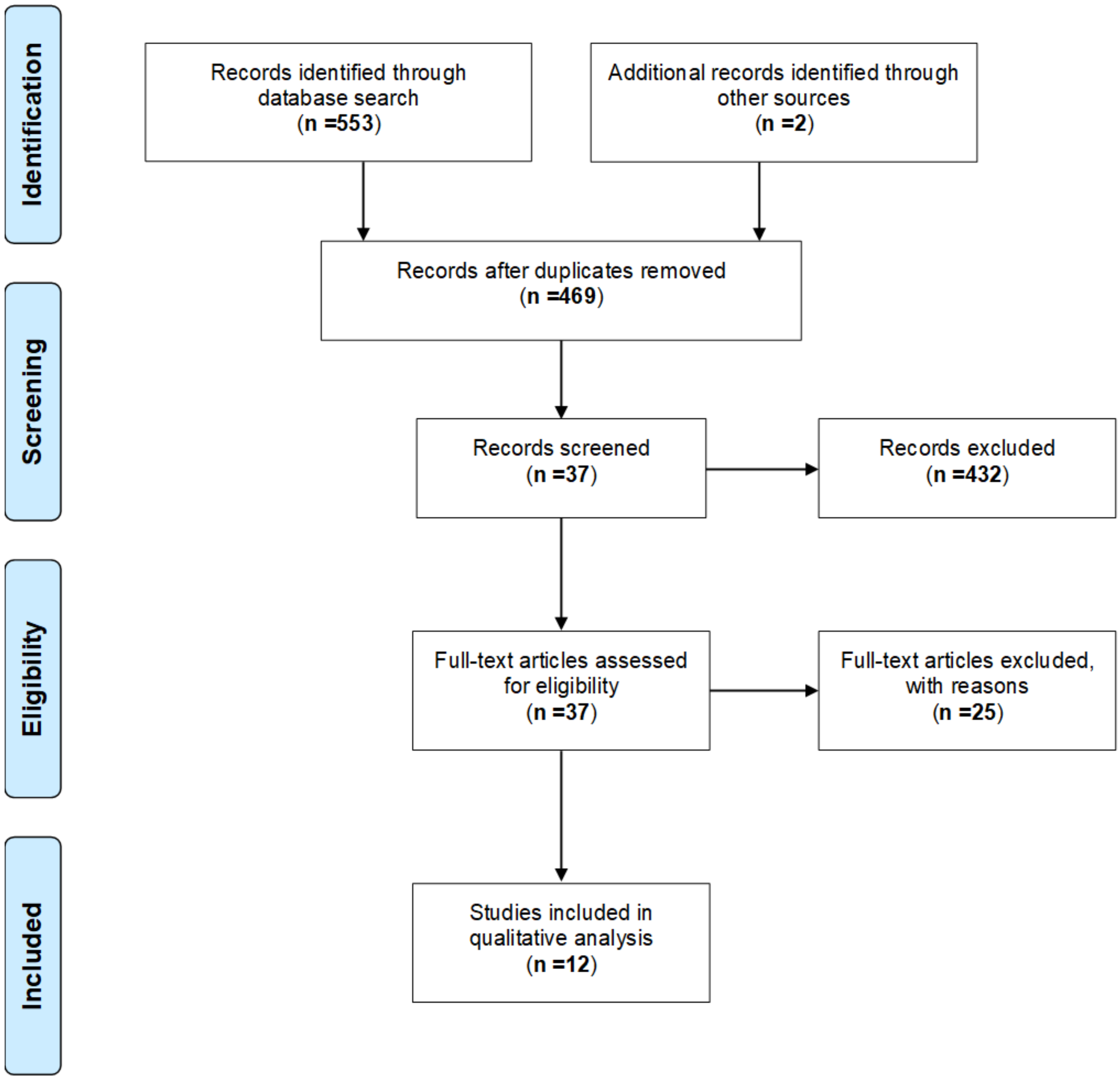

Figure 5 Search and selection process for systematic review according to PRISMA.[135]

Table 1 Quality of the study on the PEDro scale.[136]

	Study	1[a]	2	3	4	5	6	7	8	9	10	11	Total
1	Amirad et al. [144]	✓	-	-	✓	-	-	-	✓	✓	✓	✓	5
2	Dua et al. [145]	✓	-	-	-	-	-	-	-	-	✓	✓	2
3	Hedlund et al. [146]	✓	-	-	-	-	-	-	✓	✓	✓	✓	4
4	Jacobsen et al. [147]	✓	-	-	-	-	-	-	✓	-	-	✓	2
5	Longmuir et al. [148]	✓	✓	✓	✓	✓	-	✓	✓	-	✓	✓	8
6	Moalla et al.* [138]	✓	✓	-	✓	-	-	✓	✓	-	✓	✓	6
7	Morrison et al.* [139]	✓	✓	-	✓	-	-	-	-	✓	✓	✓	5
8	Sandberg et al.* [140]	✓	✓	✓	✓	-	-	-	✓	-	✓	✓	6
9	Stieber et al. [149]	✓	-	-	✓	-	-	-	✓	✓	✓	✓	5
10	Westhoff-B. et al.* [141]	✓	✓	-	✓	-	-	✓	-	✓	✓	✓	6
11	Winter et al.* [142]	✓	✓	✓	✓	-	-	-	✓	✓	✓	✓	7
12	Bhasipol et al. [150]	✓	-	-	✓	-	-	-	✓	✓	✓	✓	5

1 Eligibility criteria and source of participants; 2 random allocations; 3 concealed allocations; 4 baseline comparability; 5 blinded participants; 6 blinded therapists; 7 blind assessors; 8 adequate follow-up; 9 intention-to-treat analysis; 10 between-group comparisons; 11-point estimates and variability, [a] Item 1 does not contribute to the total score; - Not applicable, * Rating PEDro group.

Table 2 Studies characteristics**.**

Study	CHD Patients	**Diagnosis** [n]	**Age** *[years] mean ± SD (range)*	**Intervention groups** *n (male, female)* *Intervention*	*Control*	**Outcome measures**	**Drop out** *[% of all partici-pants]*	**Overall training participated** *[%]*	**Results**
1 Amiard et al. 2008 [144]	Children/ adolescents	**I:** single ventricle with pulmonary valve stenosis (3); pulmonary valve atresia with intact septum (5); ToF (5); TGA (5); ASD (5) **C:** healthy controls	**I:** 15 ± 1.4 (N/A) **C:** 16 ± 1.33 (N/A)	23 (13 m;10 f)	12 (7 m; 5 f)	CPET (VO2, workload in Watt, VE', and HR) at dyspnea threshold (DT), ventilatory threshold (VT).	no	N/A	No effect of exercise on relationship between DT and VT
2 Dua et al. 2010 [145]	Adults	**Group I:** patients, NYHA class 1 **Group II:** patients NYHA class 2 **Group III:** NYHA classes 3 and 4	31.7 ± 10.9 (18-63)	I: 21 (13 m, 8 f) II: 16, (10 m, 6 f) III: 13, (10 m, 3 f)	-	Treadmill test, QoL (PAQ, SF-12; SWLS; PSPP-scf), PA (Actigraph®, Caltrac®) activity diary.	11 [18]	N/A	Gentle graded exercise-training (walking) improves QoL, exercise capacity, and habitual PA levels.
3 Hedlund et al. 2018 [146]	Adolescents	**I:** Fontan Circulation **C:** healthy controls	**I:** 14.2 ± 3.2 (N/A) **C:** 13.6 ± 3.5 (N/A)	30 (16 m; 14 f)	25 (12 m, 13 f)	6MWT (m) HR, CPET, QoL (PedsQL Child, PedsQL Parent), self-reported exercise (min/week, average intensity on Borg).	I: 2 C: 2 [7.3]	N/A	Structured individualized training program can improve submaximal exercise capacity and QoL in short-/long-term
4 Jacobsen et al. 2016 [147]	Children	Dominant right ventricle (8), dominant left ventricle (5), biventricular anatomy (1)	N/A (8-12)	14 (8 m, 6 f)	-	O_2 saturation, BP, and HR (resting/post-shuttle run test), physical function HRQOL (PedsQL), exercise capacity (20m shuttle run test).	1 [7.1]	100	PA program is safe and feasible, proxy reported HRQOL and objective measures of exercise capacity improved significantly

AS, aortic valve stenosis; ASD (I/II), atrial septum defect (primum, secundum); AVSD, atrioventricular septal defect; BP, blood pressure; C, Control Group; ccTGA, congenitally corrected transposition of the great arteries; CHD, congenital heart disease; CHD-TAAQoL, CHD-TNO/ AZL adult quality of life; CMRI, cardiac magnetic resonance imaging; CoA, coarctation of the aorta; CPET, cardiopulmonary exercise test; CSAPPA, Children's Self-Perceptions of Adequacy in and Predilection for Physical Activity Scale; HLHS, hypoplastic left heart syndrome; HR, heart rate; HRPF, health-related physical fitness; HRQoL, health-related QoL; I, Intervention Group; MVC, maximal voluntary contraction; MVPA, moderate to vigorous physical activity; 6MWD, 6 min walking distance; 6MWT, 6 min walk test; N/A, not applicable; NIRS, near-infrared spectroscopy; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; PA, physical activity; PAQ, Physical Activity (self-efficacy) Questionnaire; PDA, patent ductus arteriosus; PS, pulmonary valvular stenosis; PSPP-scf, physical self-perception profile-short clinical form; QoL, quality of life; RV, right ventricle; SF-36, Short Form-36 Health Survey; SWLS, Satisfaction with Life Scale; TAC, truncus arteriosus communis; TAPVC, total anomalous pulmonary venous connection; TCPC, total cavopulmonary connection; TGA, transposition of the great arteries (arterial switch and mustard/senning repairs); ToF, Tetralogy of Fallot; VE, minute ventilation; VSD, ventricular septal defect.

Continued **Table 2** Studies characteristics.

5 Longmuir et al. 2013 [148]	Children	HLHS (20), tricuspid atresia (10); double-inlet left ventricle (14); pulmonary atresia (4); double-outlet right ventricle (13)	I 9.3 ± 1.3 (N/A) II 8.6 ± 2.0 (N/A)	I 30(17 m, 13 f) II 31 (19 m, 12 f)	-	PA (accelerometers, log sheet, physical function assessment, HRPF, HR, BP, O_2 consumption, CPET, CSAPPA.	7 [11.5]	50	Activity education and prescription are effective for maintaining MVPA and improving gross motor skills, exercise capacity, and fitness.
6 Moalla et al. 2012 [138]	Children/ Adolescents	ToF (5), TGA (5). ASD (4), pulmonary atresia (4)	TG: 13.0 ± 1.4 (N/A) CG: 12.8 ± 1.3 (N/A)	10	8	CPET, MVC and muscle endurance, muscle oxygenation (MO_2) (NIRS).	N/A	N/A	Individualized training at VT enhances muscular strength and endurance performance (MO_2) of the vastus lateralis muscle during exercise and recovery
7 Morrison et al. 2013 [139]	Adolescents	AS, pPS, CoA, VSD, ASD I/II, AVSD, PS, PDA, TAPVC, TGA, TAC, ToF, pulmonary atresia; HLHS, tricuspid atresia, RV hypoplasia	15.6 ± 2.27 (N/A)	72 (48 m, 24 f)	71 (38 m, 33 f)	Self-rate activity questionnaire, exercise stress test (EST), ECG, blood-pressure, oxygen saturation, day-to-day activity (Actigraph).	I: 10 C: 32 [29.4]	N/A	Exercise is feasible and beneficial. Maintenance of activity, psychological well-being, and promotion of good lifestyle choices are key elements for future programs.
8 Sandberg et al. 2017 [140]	Adults	ToF (5), ccTGA (3), d-TGA (5), TCPC (5), pulmonary atresia (2), complete atrioventricular septal defect (1), Ebstein (1), miscellaneous (1)	I: 31.3 ± N/A (N/A) CG: 26.3 ± N/A (N/A)	13 (8 m, 5 f)	10 (4 m, 6 f)	CPET, EuroQol (self-reported), vertical visual analogue scale (EQ-VAS), Hospital Anxiety, and Depression scale (HADS), exercise Self-Efficacy Scale (ESE).	I: 3 C: 0 [11.6]	79	Interval exercise training increased endurance capacity at 75% of peak workload by 12 minutes as well as peak exercise capacity

AS, aortic valve stenosis; ASD (I/II), atrial septum defect (primum, secundum); AVSD, atrioventricular septal defect; BP, blood pressure; C, Control Group; ccTGA, congenitally corrected transposition of the great arteries; CHD, congenital heart disease; CHD-TAAQoL, CHD-TNO/ AZL adult quality of life; CMRI, cardiac magnetic resonance imaging; CoA, coarctation of the aorta; CPET, cardiopulmonary exercise test; CSAPPA, Children's Self-Perceptions of Adequacy in and Predilection for Physical Activity Scale; HLHS, hypoplastic left heart syndrome; HR, heart rate; HRPF, health-related physical fitness; HRQoL, health-related QoL; I, Intervention Group; MVC, maximal voluntary contraction; MVPA, moderate to vigorous physical activity; 6MWD, 6 min walking distance; 6MWT, 6 min walk test; N/A, not applicable; NIRS, near-infrared spectroscopy; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; PA, physical activity; PAQ, Physical Activity (self-efficacy) Questionnaire; PDA, patent ductus arteriosus; PS, pulmonary valvular stenosis; PSPP-scf, physical self-perception profile-short clinical form; QoL, quality of life; RV, right ventricle; SF-36, Short Form-36 Health Survey; SWLS, Satisfaction with Life Scale; TAC, truncus arteriosus communis; TAPVC, total anomalous pulmonary venous connection; TCPC, total cavopulmonary connection; TGA, transposition of the great arteries (arterial switch and mustard/senning repairs); ToF, Tetralogy of Fallot; VE, minute ventilation; VSD, ventricular septal defect.

Continued **Table 2** Studies characteristics.

9 Stieber et al. 2012 [149]	Toddlers	ASO: arterial switch operation for transposition of the great arteries (10); SCPC: superior cavopulmonary connection for palliation of the functional single ventricle (10)	ASO: 18.1 ± 3.9 [months] (N/A); SCPC: 18.0 ± 4.3 [months] (N/A)	ASO: 10 (7 m, 3 f); SCPC: 10 (8 m, 2 f)	-	Open-ended interviews with parents (feasibility program)- neurodevelopmental level ->Peabody developmental motor scale-version 2 (PDMS-2).	0	0-100 but only 13 families (65%) provided information here	Play-based rehabilitation program is feasible and helps post-SCPC to increase to an age-appropriate developmental rate. ASO toddlers in the current surgical era have age-appropriate motor skills.
10 Westhoff-B. et al. 2013 [141]	Adults	D-transposition of the great arteries	I: 29.9 ± 3.1 (N/A); CG: 28.6 ± 3.1 (N/A)	24 (13 m; 11 f)	24 (18 m, 6 f)	ECG, QoL (Kansas City Cardiomyopathy Questionnaire, CMRI, and echocardiography, CPET, blood sample.	8 [16.7]	67.5	Aerobic exercise training can be safely performed. Continuous physical training improves exercise capacity and NYHA class.
11 Winter et al. 2012 [142]	Adults	TGA (39), ccTGA (29)	I: 31 ± 10 (N/A); CG: 34 ± 11 (N/A)	24 (9 m, 15 f)	22 (14 m, 8 f)	CPET, serum NT-pro BNP levels, QoL (SF-36, CHD-TAAQOL).	I: 4 C: 4 [14.8]	N/A	Exercise training improves exercise capacity.
12. Bhasipol et al. [150]	Adults	Eisenmenger's syndrome (4); TOF with palliative shunt (1); single ventricle (2); Other (truncus arteriosus type IV, pulmonary atresia with VSD, ccTGA with VSD) (4)	I: 30.9 ± 10.2 (N/A); C: 38.1 ± 13 (N/A)	11 (6 male, 5 female)	22 (7 male, 15 female)	CPET, 6MWD	0	N/A	Hybrid exercise intervention showed significant benefit in improvement of exercise capacity

AS, aortic valve stenosis; ASD (I/II), atrial septum defect (primum, secundum); AVSD, atrioventricular septal defect; BP, blood pressure; C, Control Group; ccTGA, congenitally corrected transposition of the great arteries; CHD, congenital heart disease; CHD-TAAQoL, CHD-TNO/ AZL adult quality of life; CMRI, cardiac magnetic resonance imaging; CoA, coarctation of the aorta; CPET, cardiopulmonary exercise test; CSAPPA, Children's Self-Perceptions of Adequacy in and Predilection for Physical Activity Scale; HLHS, hypoplastic left heart syndrome; HR, heart rate; HRPF, health-related physical fitness; HRQoL, health-related QoL; I, Intervention Group; MVC, maximal voluntary contraction; MVPA, moderate to vigorous physical activity; 6MWD, 6 min walking distance; 6MWT, 6 min walk test; N/A, not applicable; NIRS, near-infrared spectroscopy; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; PA, physical activity; PAQ, Physical Activity (self-efficacy) Questionnaire; PDA, patent ductus arteriosus; PS, pulmonary valvular stenosis; PSPP-scf, physical self-perception profile-short clinical form; QoL, quality of life; RV, right ventricle; SF-36, Short Form-36 Health Survey; SWLS, Satisfaction with Life Scale; TAC, truncus arteriosus communis; TAPVC, total anomalous pulmonary venous connection; TCPC, total cavopulmonary connection; TGA, transposition of the great arteries (arterial switch and mustard/senning repairs); ToF, Tetralogy of Fallot; VE, minute ventilation; VSD, ventricular septal defect.

Table 3 Interventions characteristics.

	Study	Total intervention duration [weeks]	Type of exercise	Frequency/ week	Time per session	Intensity	Training execution	Exercise verification
1	Amirad et al. [144]	8	Cycle ergometer	3	45 min (10 min warm-up, 30 min interval of 10 min exercise and 5 min recovery, 5 min cool-down	Corresponding to personal DT (HR corresponding to DT ± 5 beats	Home-based	HR monitor data analysis software each week after three sessions
2	Dua et al. [145]	12	Individualized gentle walking on flat, walking time increased by 10% each week	5	<3 METS 5-10 min 3-5 METS: 10-20 min >5 METS: 20-30 min	Depending on METS	Home-based	Activity diary, 2/7 days telephonic contact
3	Hedlund et al. [146]	12	Endurance training based on subjects of weekly-organized physical exercise (jogging etc.)	2	45 min	Submaximal level	Home-based/ Supervised	Instructor-led, logbook with type of activity, duration, and intensity (Borg scale)
4	Jacobsen et al. [147]	12	Formalized in-person dynamic and static exercise (DVD and paper handout)	3-4	45 min	Moderate-to-high intensity physical activity.	Home-based	Fit-bit (steps, distance, etc.), daily activity log in a journal, scheduled telephone call
5	Longmuir et al. [148]	12	1. Encourage physically active play with friends and family (e.g., Frisbee, etc.) 2. Child's/family's matched readiness for change in self-directed PA (games, stories, websites)	3-4	45 min	Not designed to provide a fitness training effect, and did not specify exercise intensity.	Parent-lead, Home/ Community-based design	Mid-month contact to get feedback and encourage compliance
6	Moalla et al. [138]	12	Stationary ergocycle	3	45 min (10-min exercise and 5-min active recovery interval training, 10-min warm-up and 5-min cool-down	HR corresponding to the VT of each subject assessed at the initial CPET.	Home-based	Pulse monitor for target exercise intensity, assisted by a physical education teacher to ensure exercise performance. Pulse monitor for appropriate intensity and duration

ACHD, adult congenital heart disease; CPET, cardiopulmonary exercise test; DT, dyspnoea threshold; HR, heart rate; METs, metabolic equivalents; N/A, not applicable; PA, physical activity; PDMS-2, Peabody Developmental Motor Scale-version 2; THR, training heart rate; VT, ventilator threshold

Continued **Table 3** Interventions characteristics.

7	Morrison et al. [139]	24	Self-implemented exercise-training plan	3	45 min	N/A	Home-based	Contact once a month to check on progress with exercise plan
8	Sandberg et al. [140]	12	Interval exercise training on cycle ergometer.	3	42 min (8 min warm-up; Intervals (5 min) separated by active recovery of 3 min 1-2 week: 3 intervals at THR; After week 2: 4 intervals at THR.	1-2 week: Training heart rate (THR) 75-80%; After week 2 Intervals at THR 75-80% warm-up/ recovery without or very low load	Home-based	HR during training was transferred to a personal web page accessible by physiotherapist and participant. Weekly contact by phone to promote compliance, provide feedback, or increase training time if necessary.
9	Stieber et al. [149]	10	Play-based activities (child's developmental age and PDMS-2 score). Two motor developmental goals as target activities for each 2-week period. Parents engage child for at least one out of six play-based activity options	7	10-20 min	N/A	Home-based parent-led, play-based	Biweekly contact of parents by investigators to assess child's progress and provision of new activities and to remind.
10	Westhoff-B. et al. [141]	24	Cycle ergometer	3 to 5	30-150 min -Week 1-3: 3x 10 min -Week 4-6: 3x15 min -Week 10-12: 5x20 min -Week 13–24: x30 min	HR controlled training at 50% of VO2peak	Home-based	Heart rate monitors. Patients were advised to document heart rate, number, and duration of training units. In order to optimize adherence to the training protocol, patients received weekly phone calls.
11	Winter et al. [142]	10	Interval training of step aerobics	3	42 min (5 min warm-up, 32 min interval training of 5x4 min alternated with 4x3 min, 5 min cool-down	HR rate controlled interval training (60-90% of max. HR)	Home-based	To improve compliance with the training protocol and to ensure safety, each patient received a weekly email asking them about their progress. Patients who did not respond to this email were contacted by telephone.
12	Bhasipol et al. [150]	12	treadmill walking and bicycling	1 to 5	30 minutes	target heart rate (HR) at 40%-70% of HR	Hospital-based phase + Home-based phase	Home pulse oximeters to reach individual target HR. Once-a-week telephone call by ACHD nurses and video call by cardiology fellow for monitoring the compliance of exercise training and checking the complications of exercise.

ACHD, adult congenital heart disease; CPET, cardiopulmonary exercise test; DT, dyspnoea threshold; HR, heart rate; METs, metabolic equivalents; N/A, not applicable; PA, physical activity; PDMS-2, Peabody Developmental Motor Scale-version 2; THR, training heart rate; VT, ventilator threshold.

Table 4 Results of the main outcomes stratified according to age groups.

	Study	Exercise capacity (pVO2)	Walking distance/ time	PA	HRQoL	Muscular strength/endurance	Motor ability
				infants/children/adolescents			
1	Amirad et al. [144]	►	-	-	-	-	-
3	Hedlund et al. [146]	►	▲	▲	▲	-	-
4	Jacobsen et al. [147]	▲	▲	►	▲	-	-
5	Longmuir et al. [148]	►	-	►	-	-	-
6	Moalla et al. [138]	-	-	-	-	▲	-
7	Morrison et al. [139]	▲	-	▲	-	-	-
9	Stieber et al. [149]	-	-	-	-	-	►
				adults			
2	Dua et al. [145]	-	▲	▲	▲	-	-
8	Sandberg et al. [140]	►	-	►	►	-	-
10	Westhoff-B. et al. [141]	▲	-	-	►	-	-
11	Winter et al. [142]	▲	-	-	►	-	-
12	Bhasipol et al. [150]	►	▲	-	-	-	-

► no improvement; ▲ improvement; - Not applicable, **pVO_2** peak oxygen uptake; **PA** physical activity; **HRQoL** health-related quality of life.

The success and feasibility of supervised and guided exercise interventions seem to be obvious. However, there is a need for safe and feasible movement concepts that can be carried out independently of time and place. In particular, the aspect of barrier-free participation and yet all the advantages of supervised guidance should be considered and implemented as far as possible. Basics of training control such as training intensity, -volume, or -duration should be sufficiently manageable.

The majority of screened interventions primarily aimed at improving cardiovascular parameters. The interventions often focused on endurance, some of them using sports equipment such as bicycle ergometers. The exercise commonly lasted180 minutes per week but this time scale can become a burden for someone who has not done regular sports before. Nevertheless, interventions should have a long-term and sustainable effect, which is likely to be difficult if they are scheduled for three months.

All these preliminary considerations led to the next part of this dissertation (**Figure 4**).

Apart from the registry of the study protocol, the exercise intervention also had to be prepared accordingly. For this purpose, a catalog of all relevant exercises was first developed, divided into three main areas: warm-up, main part, and cool down (Appendix). Exercises of the main part further differentiated into body

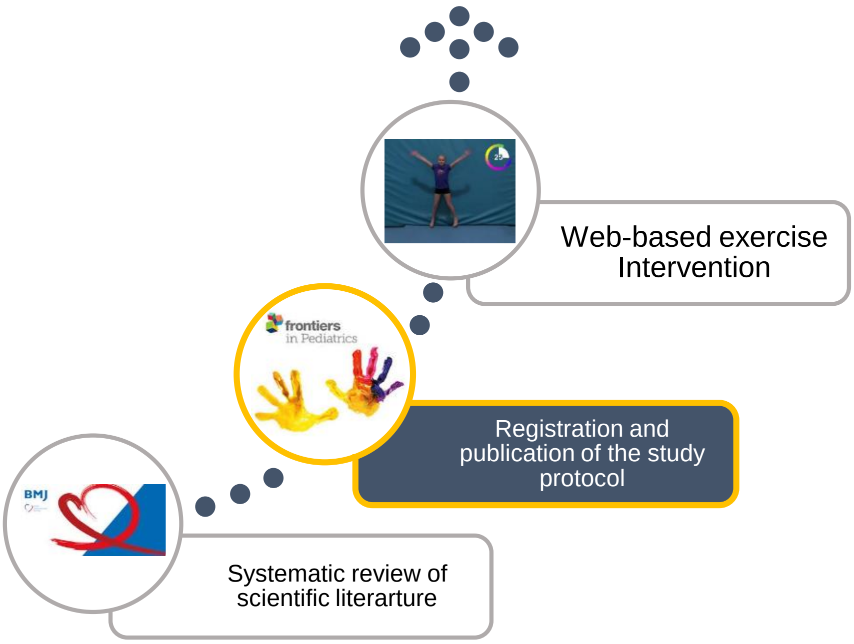

Figure 4 Preliminary methodological considerations.

regions, mainly involved, and motor requirements, such as coordination, strength, and mobility. Finally, 12 basic units could be generated, which in turn were randomly assigned to the 72 exercise units.

As the result, a new and unique training program was developed and launched under the name “One Hour a week brings mobility power and speed”. The goal should be to create long-term opportunities for young patients to take responsibility for their heart health in a familiar home environment. However, they must be made aware of this at an early age and should be provided with suitable resources. The chances of success could be increased if additional sports equipment and materials can be avoided and a virtual training partner is available. Shorter training units with attractive content could reduce the additional time required but also allow a lower barrier to regular exercise.

These and additional preliminary considerations had to be made prior to the start of the web-based exercise intervention. The resulting publication is presented in the next section.

2.2 Web-Based Motor Intervention to Increase Health-Related Physical Fitness in Children with Congenital Heart Disease: A Study Protocol [161]

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Published in: **Frontiers in Pediatrics** (DOI: https://doi.org/10.3389/fped.2018.00224)

Individual contribution:

The PhD candidate is the principal author of this paper. He designed the training sessions, edited the videos, and integrated them into the web interface. He was further responsible for technical support and supervised each participant throughout the whole intervention. PD Dr. Jan Müller revised the manuscript and Prof. Dr. Renate Oberhoffer-Fritz, and Prof. Dr. Peter Ewert did the final proof of the manuscript. The PhD candidate and PD Dr. Jan Müller processed the submission procedure until publication.

Abstract

Objective: Exercise interventions are underutilized in children with congenital heart disease (CHD) especially when the primary outcome is not peak oxygen uptake. Most of the studies are restricted to low sample size and proximity of the patients to the study centers. Now eHealth approaches bear a promising but also challenging opportunity to transmit such intervention programs to participants and check progress and compliance from remote. This study will aim to improve health-related physical fitness (HRPF) with a 24-week web-based exercise intervention.

Methods and Design: The current study is planned as a randomized control trial (RCT) with a crossover design and the aim to improve functional outcome measures. It also estimates adherence and feasibility in patients with CHD in this web-based exercise/motor intervention over 24 weeks. The primary outcome will be the improvement of HRPF. Secondary outcomes are, functional and structural arterial stiffness measures and health-related quality of life. Thus, 70 children from 10 to 18 years with CHD of moderate and complex severity will be recruited and allocated randomly 1:1 in two study arms after baseline testing for their HRPF, arterial stiffness measures, and health-related quality of life. For 24 weeks, participants in the intervention arm will receive three weekly exercise video clips of 20min each. Every video clip comprises 20 child-oriented exercises which have to be executed for 30 s followed by a recovery period of 30 s. Each session will start with 3–4 warming-up exercises, followed by 10–12 strength and flexibility exercises, and ending with 3–4min of cool down or stretching tasks. Continuous video clips will be streamed from a web-based e-learning platform. The participant simply has to imitate the execution and follow some short advice. After each session, a brief online survey will be conducted to assess perceived exertion and feasibility.

Discussion: The study will help to determine the efficacy and applicability of a web-based exercise intervention in children with CHD regarding functional outcome measures. In addition, it will outline the effectiveness of remote monitoring, which provides a cost-effective approach to reach patients with CHD that are low in prevalence and often do not live close to their tertiary center.

Trial Registration: https://ClinicalTrials.gov Identifier: NCT03488797.

Background

Children with congenital heart disease (CHD) show reduced motor competence or motor ability [13,162-164] as well as limitations in fine and gross motor skills. [76-78] These skill-based limitations from early infancy are tracked into adulthood with further negative effects on health-related physical fitness (HRPF) and muscle strength.[79-82]That those limitations still exist in the vast majority of children with CHD outline recent projects on health-related physical fitness (HRPF) and cardiovascular health.[18,19,132,165-167]
These circumstances should in general be a reason to worry and a starting signal for exercise promotions and interventions to overcome such deficits to facilitate normal social integration and school sports participation as early as possible. Unfortunately, a review from 2013 outlines that exercise interventions are still underutilized, because of the relatively low prevalence of single types of CHD and the proximity to the study centers.[26] One drawback is that the primary outcome of those studies always refers to improvements in peak oxygen uptake, while any forms of motor-related competences are of minor interest. This is probably the case because motor-related competences do not represent a hard clinical endpoint like parameters derived from cardiopulmonary exercise testing.[168-170] Another drawback refers to the willingness and availability of the parents to escort their children to the study centers.
Within the last years, digitalization has also shaped the field of medicine and many studies on eHealth and communication technology-based interventions for promoting physical activity (PA) show remarkable results.[27] The new appealing possibility to transmit, conduct, and control interventions from remote is also promising for studies in the field of patients with CHD. It is now possible to involve children with long distances to the study center to realize studies that otherwise would fail due to sample size. Currently, children and adolescents grow up to be “digital natives” who are even more familiar with handling and executing app-based tasks, than dealing with paperwork. In addition, communication via social media platforms becomes more and more appropriate to monitor the study progress and maintain study compliance, instead of classic phone calls.
In patients with CHD, eHealth is largely unexplored with only one published study on physical exercise on aerobic fitness so far.[64,171] Therefore, we have launched a randomized controlled trial (RCT) that aims to improve functional outcome measures, primarily HRPF, in children and adolescents with CHD via a tailored web-based exercise/motor intervention over 24 weeks. That article describes the study protocol in detail.

Methods

Design and participants

The current study is planned as a randomized control trial (RCT) with a crossover design and the purpose to improve functional outcome measures in patients with CHD via a web-based exercise/motor intervention over 24 weeks. The treatment scheme and data collection are presented in **Figure 6**. According to the inclusion and exclusion criteria outlined in **Table 5**, 70 children will be recruited and allocated randomly 1:1 in the two study arms after baseline testing. After 24 weeks, there will be a re-assessment of the clinical measurements.

The accordance of the Declaration of Helsinki (revision 2008) and the Good Clinical Practice Guidelines is the basis of this upcoming study. The study protocol is already approved by the ethical board of the Technical University of Munich (project number: 130/17S). All children and their guardians will provide written informed consent. The trial is already registered at ClinicalTrials.gov (NCT03488797).

Intervention

The motto of the exercise/motor intervention is “One Hour a Week, Brings Mobility, Power and Speed” which refers to the weekly training volume of 60 minutes. These 60 minutes are separated into 3 weekly sessions of 20 minutes each. The intervention is set up for 24 weeks (approximately 6 months), resulting in a total of 72 exercise sessions (3 sessions per week over 24 weeks) for each participant.

Each session comprises 20 child-oriented exercises with a focus to increase strength and flexibility. Exercises are executed for 30 seconds followed by a recovery period of 30 seconds. Each session starts with 3 to 4 warming-up exercises, followed by 10 to 12 strength and flexibility exercises, and ending with 3 to 4 cool down or stretching tasks.

All exercise sessions are continuous video clips transmitted to the participants via the web-based e-Learning platform Einstein (https://einstein.costner.is). The participant simply has to imitate the execution and follow some short advice. For a better orientation, a timer in the upper right corner displays the duration of exercise and the time of recovery. Beep signals indicate the last 3 seconds of the exercise and recovery period.

After each session, the screen will jump to a short online survey. Participants will give a quick report on perceived exertion (Borg scale) and the feasibility of the actual session. The investigator can thereby monitor adherence rate and, in case of lacking compliance, intervene via email or telephone calls. The three video clips will be available for one week (Monday to Sunday) and the participant is free to choose when to train. At the end of a week, all sessions will be erased from the account and replaced by new 3 sessions. That procedure will be repeated over the target 24 weeks.

Clinical measurements

All of the clinical measurements at baseline, short term (after 24 weeks of intervention and control group), and long-term (48 weeks after baseline) follow-up (**Figure 6**) will be conducted in the outpatient clinic of the German heart center in Munich.

Health-related physical fitness (HRPF)

HRPF will be tested by five different tests of the FITNESSGRAM® [70] test battery in a standardized order. The tests will be supervised by an experienced sports exercise physiologist.

- **Curl-Up**: abdominal strength and muscular endurance
  Execution: supine position, flexed knees with an angle of around 140° and feet placed on the ground. Arms stretched out beside the body. The upper body moves slowly towards the knees and afterwards back to the ground.
  Assessment: Score of valid curls-ups.
- **Push-ups**: upper body strength and muscular endurance
  Execution: prone position, with stretched back and legs. Arms straight under the shoulders pushing the body up and down.
  Assessment: Score of valid push-ups.
- **Shoulder stretch**: upper arm and shoulder girdle flexibility
  Execution: Hands clenched into fists. Bring fists together as close as possible behind the back. Avoid hollow back.
  Assessment: Distance of the knuckles of the forefingers. Both sides.
- **Sit and Reach**: hamstring flexibility
  Execution: Siting position, one leg stretched against a box, toes stretched upright. Other leg flexed. Reaching to the toes or further with straight arms.
  Assessment: negative or positive values in cm depending on the zero line of the box/toes. Both sides.
- **Trunk Lift**: trunk extensor strength and flexibility
  Execution: Lying outstretched in a prone position. Arms tight to the body and hands under the thighs. Lifting the upper body without bouncing while looking towards the ground.
  Assessment: Distance chin to ground in cm. Best of two trials.

Detailed information on the exercises and the test execution can be accessed from the online supplement of our recently published study in children with total cavopulmonary connection. [19]

Measures of Arterial Stiffness

Functional: pulse wave velocity (PWV) and central systolic blood pressure (cSBP)

Measures of arterial stiffness involve pulse wave velocity (PWV) and central systolic blood pressure. Functional measures of arterial stiffness play a significant role in the development of cardiovascular disease and associations to physical activity have been outlined in adult and pediatric cohorts as well.[106,107]

Therefore, the automated, oscillometric Mobil-o-Graph (I.E.M GmbH, Stolberg, Germany) is used. The measurement will be performed at the left upper arm after resting in a supine position for five minutes. Cuff size is adjusted for individual arm circumference. The inbuilt ARCSolver algorithm of the device uses a transfer function to calculate PWV and central systolic blood pressure based on the peripheral waveform.[105] The device has shown good validity and applicability in several studies, even in patients with CHD.[108,109]

Structural: carotid intima-media thickness (cIMT)

Carotid intima-media thickness (cIMT) is a marker for structural changes of the vessels and early atherosclerosis. It is shown that physical activity, in general, is associated with favorable IMT outcomes in children and adolescents.[172,173]

cIMT will be measured using B-Mode ultrasound. To minimize inter-and intra-observer variability the guidelines of the Cardiovascular Prevention Working Group of the Association for European Paediatric Cardiology are followed.[174]

The semi-automated GM-72P00A Cardiohealth Station from Panasonic (Yokohama, Japan) is used together with a linear probe of 9 MHz to assess cIMT at the arteria carotis communis. The measurements are conducted in a supine position with patients' head turned 45 degrees to the opposite of the examined side and the neck slightly tilted backward. In the first step, the neck vessels were scanned for plaques in a cross-section, afterwards, the common carotid artery was displayed in the longitudinal view.

Pictures are then taken of the cIMT on the far-wall, in the end-diastolic phase, approximately 1 cm proximal to the bifurcation in two angles on the left (210° and 240° degrees) and two angles on the right side (120° and 150° degrees).

Health-related Quality of Life (HRQoL)

The KINDL-R questionnaire is handed out to assess health-related quality of life (HRQoL). It is a common, international, and well-standardized questionnaire for evaluating children's HRQoL from a subjective perspective.[175-178] It exists in three versions according to the different age groups. In this study, the KidKINDL for children aged 7–13 years and the KiddoKINDL for children aged 14–17 years is used.

The questionnaire consists of 24 items that refer to the past week and is answered on a 5-point Likert scale (never, seldom, sometimes, often, and always). The scored items are then transferred to a total HRQoL score and six subscales (physical, emotional, self-esteem, family, friends, everyday functioning). All subscales are graded on a scale from 0–100, whereby higher values reflect better HRQoL.

Enrollment

The participants will perform the five motor tasks initially. Based on the test results of a reference cohort, LMS values were calculated according to Cole [179] using R-Studio (version 0.99.879, R-Studio Inc.) with the module extensions *gamlss* (version 3.4-8) and AGD (version 0.34). Children with CHD will be classified according to those established LMS values and z-scores displayed for each of the five tasks and HRPF z-score as the mean of the five tasks.

Participants are consecutive randomized and, when admitted to the intervention arm, start directly the week after screening for baseline characteristics with the exercise program. Every participant receives an anonymous account where 3 sessions will appear every week.

Endpoints

Primary endpoint

The primary endpoint criterion refers to an improvement of health-related physical fitness, assessed as the mean z-score of the five tests, 24 weeks (approximately 6 months) after the intervention.

Secondary endpoints

Secondary endpoints are as followed:

- Compliance (adherence) with the supervised web- and home-based intervention measured as the participation rate in the training sessions (%).
- Improvement of Central/peripheral blood pressure after 24 weeks (approximately 6 months) after the intervention.
- Improvement of Intima-media thickness after 24 weeks (approximately 6 months) after the intervention
- Improvement of health-related quality of life 24 weeks (approximately 6 months) after the intervention.
- Improvement of pulse wave velocity 24 weeks (approximately 6 months) after the intervention.

Sample size calculation

Sample size was calculated with G* (http://www.gpower.hhu.de) [180] according to the primary endpoint criterion. According to our preceding cross-sectional study, [19,115,165] a HRPF z-score of about -0.64 ± 0.9 (27^{th} percentile) was averaged in the CHD children in comparison to the healthy reference. The study aims to improve HRPF to a value of 0.0 ± 1.0 (50^{th} percentile) at the end of the intervention. With a power of 85% on a one-sided level of significance of 0.05, a sample size of 31 per group is necessary. Assuming a slight drop out of about 10% in total 70 children will be recruited and allocated randomly 1:1 in the two study arms.

Statistical methods

Difference of the HRPF z-score for each participant will be compared between both study groups using an independent two-sample t-test (if normal distributed) or Mann-Whitney U-Test (if skewed). To calculate gender-specific and group-specific differences over time, repeated ANOVA measures (if normal distributed) or Friedman-test (if skewed) will be performed. In terms of drop-out, an intention to treat analysis will be performed. Two-sided level of significance of 5% will be considered for this primary endpoint.

Discussion

The objective of this RCT is to determine the effect on HRPF and other functional outcome measures, as well as the compliance of a web-based exercise intervention in children with CHD.

Several studies in CHD have shown that participation in a physical exercise-training program is safe and improves fitness.[26,145] Unfortunately, those exercise interventions are underutilized in children with CHD, and fitness, as the primary endpoint, is mostly just determined as an improvement in peak oxygen uptake while interest in other functional measures is rare. Indeed, peak oxygen uptake may be the most important prognostic parameter for survival in patients with CHD [168-170] but it is controversial whether that importance already exists in children with CHD. The idea behind is the changing landscape of older patients with CHD that will develop acquired cardiovascular disease, such as hypertension and hyper-lipidemia.[8,181] From the perspective of primary prevention, it is, therefore, more important to shape PA behavior early in life that yields health benefits later in life. Motor skill development across childhood has proven to influence children's PA behavior beneficially later in life in many ways.[182,183] Therefore, the objective of this study refers to HRPF and other functional outcomes instead of solely peak oxygen uptake.

Several studies already have investigated the feasibility and effectiveness of a home-based exercise intervention for young and adult people with CHD.[26,132] The utility of exercise interventions for this target group is unchallenged, but in 21 studies only 621 subjects, 30 per study, were included.[26] Those small sample sizes very often lead to missing results and weak generalizability. Moreover, supervised training interventions are difficult to schedule and to conduct because of the low prevalence of patients with CHD.

To overcome those problems this study uses a web-based solution for two reasons. First, to include more patients in particular from remote areas, and second, to deliver and monitor the intervention more effective. The proposed training stimulus of 3 sessions of 20 minutes per week results in a relatively low real training volume of 30 minutes per week because the other 30 min are recovery time. Most of the studies mentioned in the comprehensive review [26] had longer durations for one training session and an overall higher workload per week but were conducted for only 12 weeks. Since this study takes twice as long we decided not to occupy the patient with intensive training. Instead, it is assumed that less work-load throughout the week leads to better long-term compliance. That is also the reason why the patient is free in performing its 3 sessions per week instead of sticking to a fixed schedule.

The biggest challenge is the monitoring of the home-based intervention. Indeed 10 of the 21 studies did not report participation rate. Commonly in a home-based intervention that is done by training logs and/or regular phone calls - a method that is inappropriate and especially uneconomical these days because they are not manageable outside a clinical study. With the electronic reporting and the possibility of tracking when training sessions were streamed it is much easier to follow compliance. In addition, auto-mated messages can be sent to the patients to remind him/her of the execution, and vice versa for the supervisor when training progress is missing. Nevertheless, it cannot entirely rule out that the patients cheat in reporting. Consumer-friendly wearable technology is a promising prospect in dealing with that issue but currently, applications that are easy to use and connected to a central server are missing.[184] Web-based or eHealth PA interventions in patients with CHD are virtually not existent. Only the PReVaiL [64,171] trial tried to assess the benefits and harms of a tailored eHealth intervention with education and individual counseling in adolescents with CHD. Unfortunately, no change in oxygen uptake, PA, and health-related quality of life occurred 52 weeks after the educational and motivational intervention. However, the most frustrating point was the low compliance with the intervention, which clearly outlined the vulnerability of those web-based approaches. Therefore, our web-based intervention will contain exercise videos for a maximum of 24 weeks to minimize the number of drop-outs. Further, each exercise session consists of 20 different exercises that won't take more than 20 minutes. This means the amount of exercise is right at a level where changes in HRPF still can be expected but former inactive people aren't overstrained with an excessive exercise amount. Nevertheless, eHealth provides easy and wide reachability at a low cost. Strategies have to be developed and evaluated to use this technique to maintain and improve clinical care in this growing cohort of patients with CHD. This study aims to understand the feasibility and compliance of those web-based studies.

Abbreviations

CHD: congenital heart disease, cIMT: carotid intima-media thickness, HRPF: health-related physical fitness, HRQoL: health-related quality of life, PWV: pulse wave velocity, RCT: a randomized controlled trial

Acknowledgment

The authors would like to thank the staff, and especially the nurses, of the outpatient apartment of the German Heart Centre for their dedicative support in this project.

This work was supported by the German Research Foundation (DFG) and the Technical University of Munich (TUM) in the framework of the Open Access Publishing Program.

Funding

This study is funded by an unrestricted grant from the "Robert-Enke-Stiftung" and the "Fördergemeinschaft Deutsche Kinderherzzentren e.V". The funders have no direct role in the study's conduct, analysis, interpretation of data, and reporting beyond approval of the scientific protocol. None of the authors had any personal or financial conflicts of interest

Authors' contributions

MM, AH, RO, PE, and JM were all involved in the development of the study protocol. JM prepared the initial draft of the manuscript. MM and AH set up the database infrastructure for the intervention. All authors read, contributed to editing, and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the ethical board of the Technical University of Munich (project number: 130/17S). All children and their guardians will provide written informed consent. The trial is registered at ClinicalTrials.gov (NCT03488797).

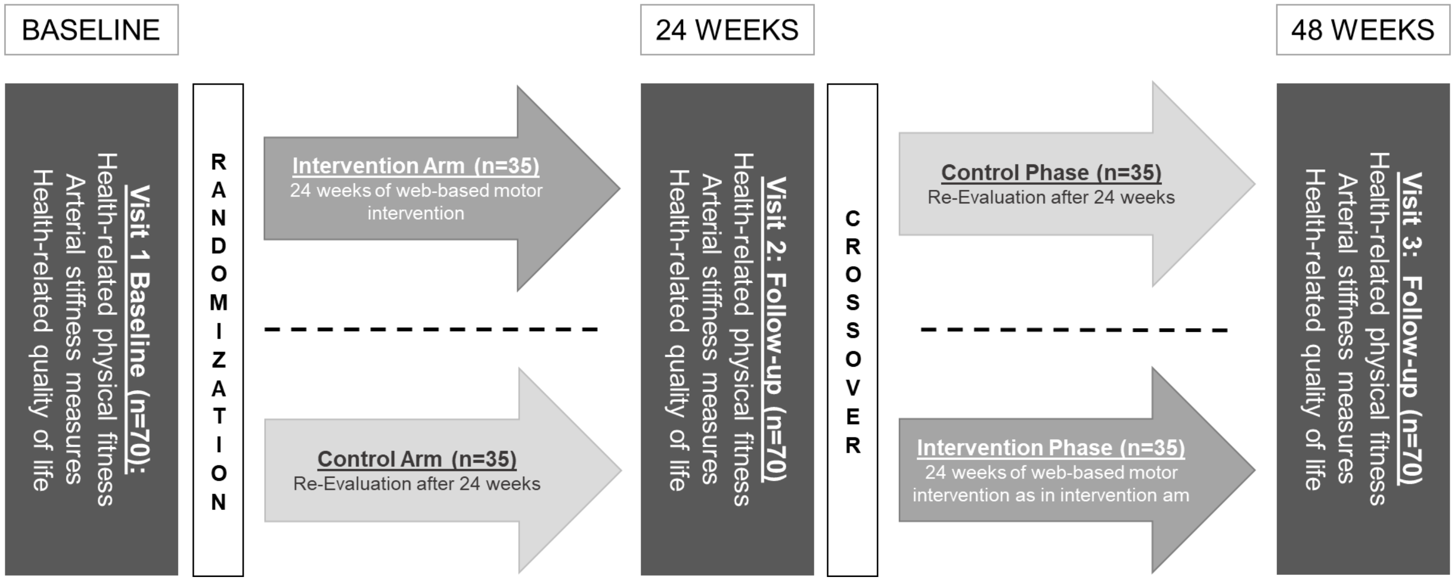

Figure 6 Study design and intervention scheme.

Table 5 Inclusion and exclusion criteria.

Inclusion criteria	**Exclusion criteria**
Age 10-18 years old	Severe Arrhythmias
CHD with moderate to complex severity according to the ACC criteria*	Severe Left Heart Failure
Health-related physical fitness <50th percentile (healthy reference)	Chromosomal anomalies and/or genetic syndromes
German-speaking	Severe physical and/or sensory impairments (hearing, visual, or psychomotor)
internet availability and an internet-capable device to use the intervention app	Elective cardiac intervention within the next 6 months following enrollment
Informed consent of parent/guardian as well as of the child	

*according to Warnes et al. Task force 1: the changing profile of congenital heart disease in adult life.[185]

3 Results and Discussion

On the one hand, training videos had to be developed independently, which included the entire process from recording and editing to the production of the final clips for the individual training sessions. On the other hand, these clips had to be implemented and further processed within the training platform. At the same time, technical support for the users as well as occasional phone calls to ensure participation and motivation had to be provided.

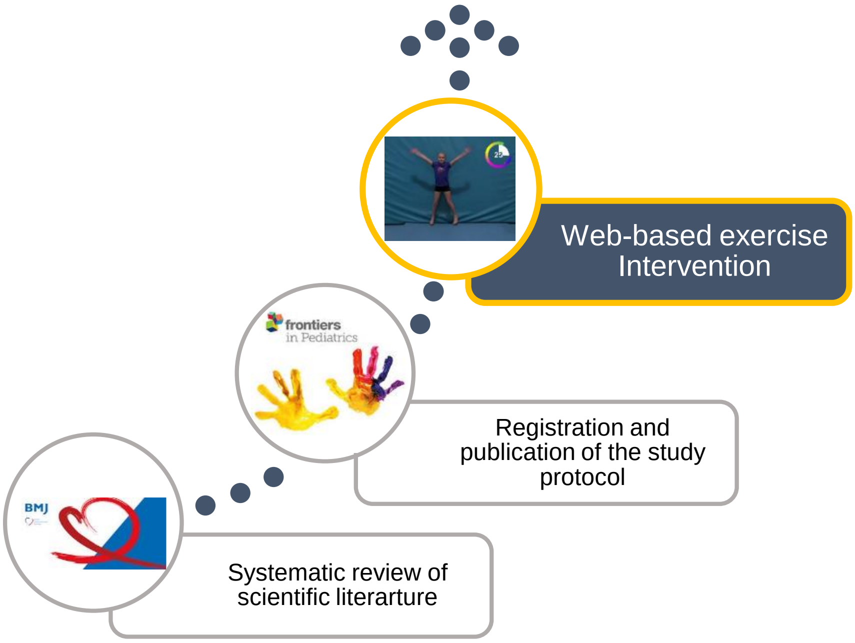

Figure 4 Preliminary methodological considerations.

Since the study kick-off in June 2018, within 14 months the last patient could be recruited to join the web-based exercise intervention "One Hour a week brings mobility power and speed". After almost two years of intense patient management, the last patient returned for the follow-up examination on June 24, 2020. During this period, 70 patients could be successfully recruited, 61 of whom appeared for follow-up in addition to their baseline examination. However, due to the outbreak of the Sars-Cov-2 pandemic in spring 2020, the outpatient clinic had to be temporarily shut down. This restricted the study schedule considerably, which posed further challenges for the termination of the randomized clinical trial. The coming section marks the final part of this dissertation (**Figure 4**). It contains further details according to the results of the 24-week web-based exercise intervention.

3.1 E-health exercise intervention for pediatric patients with congenital heart disease: a randomized controlled trial [186]

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Abbreviations: congenital heart disease (CHD), health-related physical fitness (HRPF), health-related quality of life (HRQoL), standard deviation scores (z-Score)

Published in: **The Journal of Pediatrics** (DOI:https://doi.org/10.1016/j.jpeds.2021.01.058)

Individual contribution:
The PhD candidate is the principal author of this paper. In cooperation with other examiners, he sampled the data at the German Heart Center, performed the statistical analysis of the results, and the presentation of the results. PD Dr. Jan Müller revised the manuscript and Prof. Dr. Renate Oberhoffer-Fritz, and Prof. Dr. Peter Ewert did the final proof of the manuscript. The PhD candidate and PD Dr. Jan Müller process the submission procedure and the paper is under review in “The Journal of Pediatrics”.

Abstract

Objective: To improve Health related physical fitness (HRPF) (primary outcome) and health-related quality of life (HRQoL) with a web-based motor intervention program in pediatric patients with congenital heart disease (CHD).

Study design: Overall, 70 patients (13.0 ± 2.6 years; 34% girls) aged 10 to 18 years with moderate or complex CHD severity were randomly allocated 1:1 to an intervention or control group). The intervention group trained three times per week for 20 minutes in a web-based exercise program over a period of 24 weeks. The control group followed lifestyle per usual. At baseline and follow-up HRPF was assessed via five tasks of the FITNESSGRAM® and converted to a HRPF z-score. HRQoL was assessed with KINDL® self-report questionnaire.

Results: 61 patients completed the follow-up. There was no change in total HRPF z-score (intervention group: 0.14 ± 0.38 vs. control group: 0.09 ± 0.38, p=0.560) and total HRQoL (intervention group: -1.73 ± 8.33 vs. control group: 1.31 ± 7.85, p=0.160) after 24-weeks web-based exercise intervention. This was true for all subcategories of HRPF and HRQoL. There were no adverse events associated with the web-based exercise intervention.

Conclusion: 24-weeks of web-based exercise intervention with an aimed volume of 60 minutes of exercise per week was safe but did not improve HRPF and HRQoL in children with moderate or complex CHD.

Clinical Trial Registration: clinicaltrials.gov (NCT03488797).

Introduction

Regular exercise for children with congenital heart disease (CHD) is strongly recommended by international guidelines. [20-22] However, several challenges keep these patients from pursuing an active lifestyle such as overprotection, lack of information about the correct exercise regimen, or motivation. Parental uncertainty about appropriate types and restrictions of activity is associated with more sedentary lifestyle.[187] In addition, activity restrictions and reduced exercise capacity in early childhood can influence the physical self-concept [188] and impact self-efficacy.[189] reduced gross and fine motor development and consequently reduced health related physical fitness (HRPF) are prevalent in pediatric patients with moderate and complex CHD.[18,19,166]

Health also consists of Health-related Quality of Life (HRQoL); a functional outcome reflecting patient's reported health status [190] which can be substantially worse in patients with CHD.[100] Participating in an exercise program has been associated with better HRQoL in children with CHD.[191]

Advancing digitization goes along with great potential in health care regarding eHealth solutions.[27] Web-based training formats can be contemporary, target-group oriented and allow for customization of training times. They therefore are promising alternatives to conventional training manuals or supervised training.[192]

Our randomized controlled trial (RCT) aimed to improve functional outcome measures, primarily HRPF, in children and adolescents with CHD by a 24-week web-based exercise intervention.

Methods

This study was a prospective, single-center, parallel group, randomized controlled trial performed out of the outpatient clinic of the German Heart Center Munich, Germany. It complies with the Declaration of Helsinki (revision 2008) and the Good Clinical Practice guidelines. The study protocol was approved by the local ethical board of the Technical University of Munich (project number: 130/17S), registered at clinicaltrials.gov (NCT03488797) and published in advance.[161] All guardians and participants provided written informed consent prior randomization.

From May 2018 to September 2019, all patients of the outpatient clinic of the German Heart Center Munich with moderate to complex CHD severity [185], aged 10-18 years were screened for eligibility as part of the FOOTLOOSE project (German Clinical Trials Register: DRKS00018853). Exclusion criteria were: Severe arrhythmias, severe left heart failure, planed elective cardiac intervention within the next 6 months following possible enrollment, chromosomal anomalies, genetic syndromes, and severe physical or sensory impairments (hearing, visual, or psychomotor).

For inclusion, total HRPF score had to be below the 50th percentile of a healthy reference. This reference score was based on 983 valid data sets of 2551 healthy controls (11.6 ± 2.7 years, 1424 girls) recruited from October 2012 to October 2016 within two different projects in several Bavarian schools.

G* power analysis [180] revealed a sample size of 31 in both, intervention and control group, as we aimed for an improvement of HRPF from 27th percentile (-0.64 ± 0.9) to 50th percentile (0.0 ± 1.0) after 24-weeks exercise intervention (one sided α of 0.05, 85% power). Assuming a possible dropout of 10% led us to the recruitment of a total of 70 children.

Overall, 440 patients were identified in the daily routine of the outpatient clinic (**Figure 7**) and passed baseline examination for HRPF and HRQoL; 370 out of 440 approached participants had to be excluded because they did not meet inclusion criteria (n=258) or declined to participate (n=112). The 112 patients who declined to participate did not differ concerning age (p=.249), sex (p=.844), severity (p=.547) or HRPF z-Score (p=.441) from the included patients. Finally, 70 patients with CHD (13.0 ± 2.6 years; 34% girls) were randomly allocated 1:1 to either intervention or control group using a sealed envelope. Patient's characteristics are in **Table 6**. All pre- and post-tests of the outcome parameters were conducted by one person (MM).

All subjects completed five tasks in accordance to the FITNESSGRAM® [70] in standardized order to assess HRPF. The test battery consists of curl-ups and trunk-lift to assess abdominal and truncal strength as well as push-ups for examining upper limp strength. A correct execution such as complete sitting up or 90° Flexion in the elbow and maximum number of repetitions were obligatory. The trunk lift comprised two repetitions with the best attempt used for further calculations. Shoulder stretch and sit-and-reach test were used to assess upper- and lower limb flexibility. Both of these tests were performed separately with the left and right side. Afterwards, mean scores of both sides were calculated. More detailed information about the execution of the HRPF test battery within the FOOTLOOSE project is published.[18,19]

At baseline and follow-up, participants completed the KINDL®, a generic instrument commonly used to assess HRQoL. We employed the KidKINDL® version for patients younger and the KiddoKINDL® for older than 14 years. Each version consists of 24 items which are answered on a 5-point Likert scale (never, seldom, sometimes, often and always) measuring the dimensions of physical well-being, emotional well-being, self-esteem, family, friends and school with a recall period of one week.[95,178] All items were converted into a HRQoL score ranging on a scale from 0 (worst) to 100 (best) which provides either a total HRQoL measure or sub-categorical insights.

Patients assigned to the intervention group started with a web-based exercise intervention, lasting 24 weeks, one week after baseline evaluation. Three sessions for 20 min were the target training regimen per week. Each exercise session included a video with child friendly instructions and demonstration of the different exercises. The videos served as a virtual training partner and exercise was performed simultaneously while watching the video (see online supplement). Further details can be found in the open accessible published study protocol [161] as well as in the online supplement. Training adherence and adherence were monitored and documented with a video tracking tool included in the exercise platform (https://einstein.costner.is). To enhance adherence each participant received a weekly e-mail reminder to stick with the training. In case there was no training progress for more than two weeks, participants were called to inquire about the causes. Furthermore, telephone calls between researcher and participants provided further subjective feedback about any problems with the program. The control group was instructed to go about their daily routine as usual. Final assessment of all outcomes took place at least 24 weeks after baseline evaluation in both groups.

Four participants in each study group were lost to follow-up due to personal reasons at the 24-week testing period. One participant of the control group dropped out because of interventional catheterization. Generally, there were no adverse events in association with the 24-week web-based exercise intervention.

Methods for calculating healthy reference percentiles and standard deviation scores (z-score) of HRPF have already been published.[161]

The primary analysis included all patients who completed the 24-week follow-up (per-protocol analysis).

Group differences of intervention and control group in HRPF and HRQoL from baseline to follow-up was calculated in the per-protocol analysis using independent student T-test. In addition, Pearson correlation was used to identify possible association between HRPF and exercise frequency. Effect sizes ‘r’ were classified according to Cohen.[193]

Further, intention-to-treat analysis using multiple imputations [194] was performed for the nine patients lost to follow-up (**Figure 7**). A chain of regression equations was used to obtain missing data imputed one by one using R-Studio (V.0.99.879, RStudio, INC. 2015) with the module extensions MICE (V. 3.9.0). A dichotomous grouping variable contributed to both, while handgrip strength and the five test scores were used for the HRPF total scores, and the six subdomains of HRQoL were used to generate their missing values of the total score.

As the MICE package (V.3.9.0) itself does not have a pooled t-test option, a linear regression analysis was conducted, which is the same procedure to get a pooled independent t-test in R. Therefore, a linear regression analysis with a continuous outcome variable (HRPF z-score or HRQoL total score) and an independent dichotomous variable (intervention, control group) was used to get pooled differences between the intervention and control group from baseline to follow-up in the intention-to-treat analysis. Results are presented as mean difference ± standard estimate error (SEE).

Descriptive data as well as the results of the student T-test are expressed in mean values ± standard deviation (SD). Interquartile Range (IQR) were used to express participation rate in percent of total exercise (%). All analyses were performed using R-Studio (V1.2.503, RStudio, INC. 2015) with the module ggplot2, lsmeans, emmeans. Two-sided p-values <0.05 were considered significant.

Results

Per protocol analysis revealed no improvement after 24-weeks web-based exercise training for total HRPF (intervention group: 0.14 ± 0.38 vs. control group: 0.09 ± 0.38, p=0.560) or any of the five subcategories of HRPF (**Table 7**). Further within-subject development for total HRPF is illustrated in **Figure 8**. The mean weekly exercise adherence was 33% [IQR= 8-60%]. There was no significant association between adherence rate and difference of HRPF (r=0.05 p=0.800).

There was also no improvement in total HRQoL after 24-weeks web-based exercise intervention (intervention group: -1.73 ± 8.33, control group: 1.31 ± 7.85, p=0.160). **Table 7** contains a detailed overview of the remaining HRQoL subcategories.

The intention-to-treat analysis revealed no significant differences between intervention group and control group in total HRPF (-0.04 ± 0.08 SEE, p=0.625), total HRQoL (2.58 ± 1.90 SEE, p=0.180) or any of the subcategories.

Discussion

Exercise interventions were first successfully used in children with CHD over 40 years ago.[25] a supervised approach is outdated because of the distance to tertiary centers for parents and children to attend training. Exercise interventions can improve exercise [150,195] or endurance capacity [140], even when performed in a home-based setting. Therefore, the combination of home based exercise interventions with modern eHealth approaches [29] to support patients or provide information [150] is logical. One web-based intervention investigated an eHealth approach encouraging physical activity in adolescents with CHD.[196] Klausen et al. provided a health education and individual counseling in adolescents with CHD for one hour. Over the next 52 weeks, participants received a tailored eHealth encouragement to increase physical activity via mobile application and short message service to improve oxygen uptake and HRQoL. Similar to our study they could not show any improvement in their primary outcome measures.

In contrast, we used a direct training approach [26] instead of targeting existing habits and preferences of sports activities. Our direct approach aimed to keep the time effort for our participants manageable. Furthermore, our goal was to include a variety of participants independent of their previous physical background. The total intervention time of one-hour per week seemed appropriate for participants.[144] We kept training days, location, and execution flexible. However, these aspects could also have led to a training volume or intensity, which was insufficient to achieve any effect at all.

Despite lack of guidelines our exercise frequency was the same as suggested previously [131] and the total program time of 24 weeks of web-based exercise was twice as long. In contrast, one of our sessions only lasted half of the recommended 40 minutes. This may also have affected our results and should therefore be accounted for in the interpretation.

In retrospect we speculate that the standardized training protocol was not individual enough [131,197] for the relatively wide age range of our participants to show a training effect. Furthermore, exercises might require more guidance or external supervision before starting the program.[26] This would have been especially helpful considering our patients who had reduced HRPF according to the study protocol. Sports enjoyment is a key factor that determines participation and adherence to exercise regimens.[197,198] Unfortunately, it seems that our flexible approach might have led to laziness and carelessness.

In comparison to Klausen et al. who had a dropout rate of 28%, we lost 13%. We noticed a very low adherence rate of 33% to our total 72 training days. In the PreVail study [196], a higher adherence of 57% was detected, but this was defined as two consecutive weeks arbitrarily within the 52 weeks of intervention. School stress, transition to secondary school, or the start of the first job were mentioned as reasons not to adhere to the training. In addition, time competition with existing leisure activities was another reason for younger participants for non-adherence.

Neither the study by Klausen et al. nor our study could observe an improvement of HRQoL after a web-based intervention. Both studies used questionnaires with valid psychometric properties. However, comparability of the results must be treated with caution.[97,199]

Despite the tracking function of all video activities, there was no additional movement monitoring or other verification of exercise load during the 24-weeks intervention period. In addition, patients in the control group may have been motivated similar to the intervention group, the specificity/focus of the exercise selection/intervention may not have been optimum.

Future research should investigate a combined approach of supervised and independent training to encourage behavioral change and continue to examine digital approaches that use more gamified content. Optimally, the whole family and peers, such as friends or other children and adolescents with the same limitations, could be involved in order to motivate them to exercise regularly and to improve their motor skills as well as their quality of life.

Acknowledgment

We gratefully thank the children and adolescents as well as their parents for their dedicated support of our study.

Funding

This study was funded of an unrestricted grant from the “Fördergemeinschaft Deutsche Kinderherzen e.V.”, “Robert-Enke-Stiftung” and the “Förderverein Deutsches Herzzentrum München”

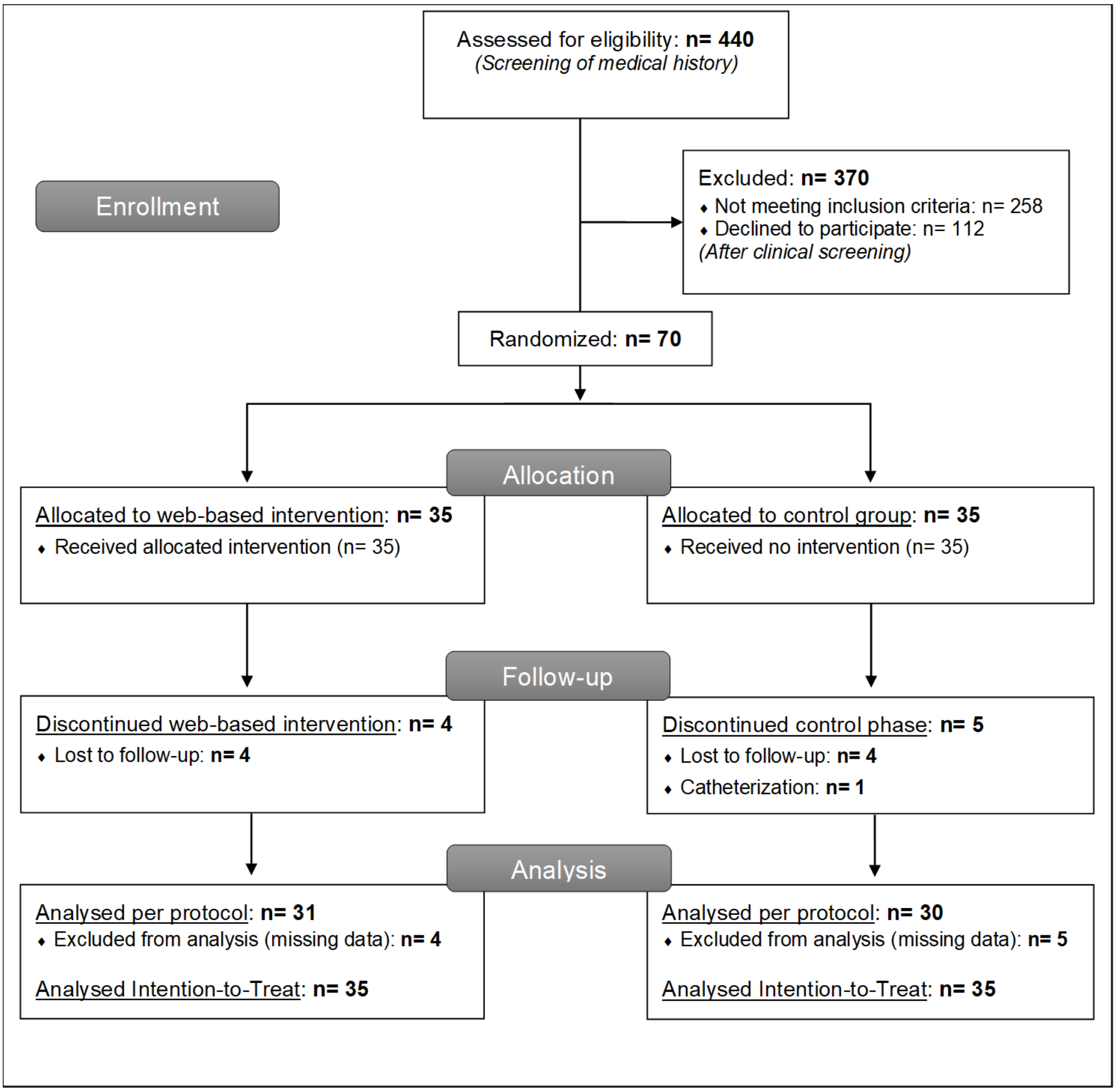

Figure 7 CONSORT Flowchart [200] enrollment and allocation study population.

Table 6 Patients characteristics of the study population.

Characteristics	**Total** *(n=70)*	**Intervention** *(n=35)*	**Control** *(n=35)*
Sex, female	24 (34%)	12 (34%)	12 (34%)
Age [*years*]	13.05 ± 2.6	13.08 ± 2.8	13.02 ± 2.4
Height [*cm*]	152.7 ± 15.1	153.7 ± 16.0	151.6 ± 14.3
Weight [*kg*]	45.4 ± 14.5	46.8 ± 14.6	44.1 ± 14.3
BMI [kg/m^2]	19.1 ± 4.2	19.3 ± 3.5	18.8 ± 4.9
BMI [*z-Score*]	-0.16 ± 1.2	0.01 ± 1.1	-0.32 ± 1.3
Waist circumference [*cm*]	67.0 ± 9.3	68.7 ± 10.4	65.4 ± 7.8
Hip circumference [*cm*]	81.4 ± 11.2	82.9 ± 10.6	79.9 ± 11.6
Severity*			
moderate	25	12	13
complex	45	23	22
Diagnosis			
Left heart obstruction	9	5	4
Right heart obstruction	23	10	13
Isolated shunts	4	1	3
TGA after arterial switch	8	3	5
Total cavopulmonary connection	16	11	5
Miscellaneous	10	5	5

BMI: Body Mass Index; *CHD severity according to ACC [185]; TGA: Transposition of the great arteries.

Table 7 Mean differences between the Intervention and Control group after 24-weeks of exercise intervention.

	Intervention Group (n=31)			*Control Group (n=30)*				
HRPF	**Baseline Evaluation**	**24 Weeks Follow-Up**	*Difference* (Mean ± SD)	**Baseline Evaluation**)	**24 Weeks Follow-Up**	*Difference* (Mean ± SD)	*Diff. IG and CG* (Mean ± SD)	**p-Value***
Total [z-Score]	-0.87 ± 0.73	-0.57 ± 0.58	0.14 ± 0.39	-0.79 ± 0.42	-0.75 ± 0.61	0.09 ± 0.38	0.33 ± 0.48	0.56
Curl-ups [z-Score]	-1.11 ± 0.84	-0.67 ± 0.98	0.30 ± 0.84	-0.81 ± 0.92	-0.57 ± 1.12	0.34 ± 0.77	0.07 ± 0.81	0.83
Trunk-lift [z-Score]	-0.84 ± 1.19	-0.40 ± 1.03	0.26 ± 0.96	-0.91 ± 0.79	-0.82 ± 0.85	0.15 ± 0.85	-0.26 ± 0.92	0.62
Push-ups [z-Score]	-0.28 ± 0.95	-0.08 ± 1.21	0.15 ± 0.97	-0.36 ± 0.71	-0.08 ± 1.03	0.21 ± 0.73	0.36 ± 0.86	0.77
Shoulder stretch [z-Score]	-1.05 ± 1.22	-0.75 ± 1.23	0.12 ± 0.62	-1.29 ± 1.09	-1.16 ± 0.98	0.14 ± 0.73	0.53 ± 0.68	0.91
Sit and reach [z-Score]	-1.09 ± 1.79	-0.96 ± 1.43	-0.10 ± 0.81	-0.60 ± 1.24	-1.10 ± 1.39	-0.40 ± 0.80	0.93 ± 1.47	0.15
HrQoL								
Total	77.20 ± 9.64	76.20 ± 9.82	-1.73 ± 8.33	76.62 ± 11.74	79.37 ± 9.32	1.31 ± 7.85	5.88 ± 8.73	0.16
Physical well-being	78.39 ± 17.17	76.11 ± 16.92	-2.90 ± 16.00	74.46 ± 17.04	76.45 ± 14.92	0.83 ± 15.28	13.07 ± 26.66	0.36
Emotional well-being	81.60 ± 9.93	84.15 ± 9.84	2.00 ± 9.32	81.60 ± 12.40	85.69 ± 12.17	3.82 ± 10.86	7.09 ± 14.35	0.50
Self-esteem	67.67 ± 16.63	64.73 ± 16.24	-4.01 ± 18.72	64.09 ± 18.73	66.04 ± 18.25	<0.01 ± 17.50	18.38 ± 25.37	0.40
Family	87.32 ± 13.08	86.85 ± 12.86	-0.43 ± 12.93	84.68 ± 21.21	88.54 ± 12.18	0.86 ± 16.93	-13.44 ± 16.78	0.74
Friends	77.50 ± 18.57	77.44 ± 19.28	-2.08 ± 19.07	79.78 ± 15.46	82.11 ± 12.24	2.23 ± 17.28	14.32 ± 24.61	0.37
School	70.71 ± 16.65	69.19 ± 16.57	-2.23 ± 16.51	74.81 ± 15.66	76.56 ± 15.92	-0.96 ± 15.78	-2.08 ± 18.19	0.77

HRPF: Health-related Physical Fitness, HRQoL: Health-related Quality of life, IG: Intervention group, CG: Control group, *Student T-Test Difference between Intervention group and Control group with p-values <0.05 considered significant.

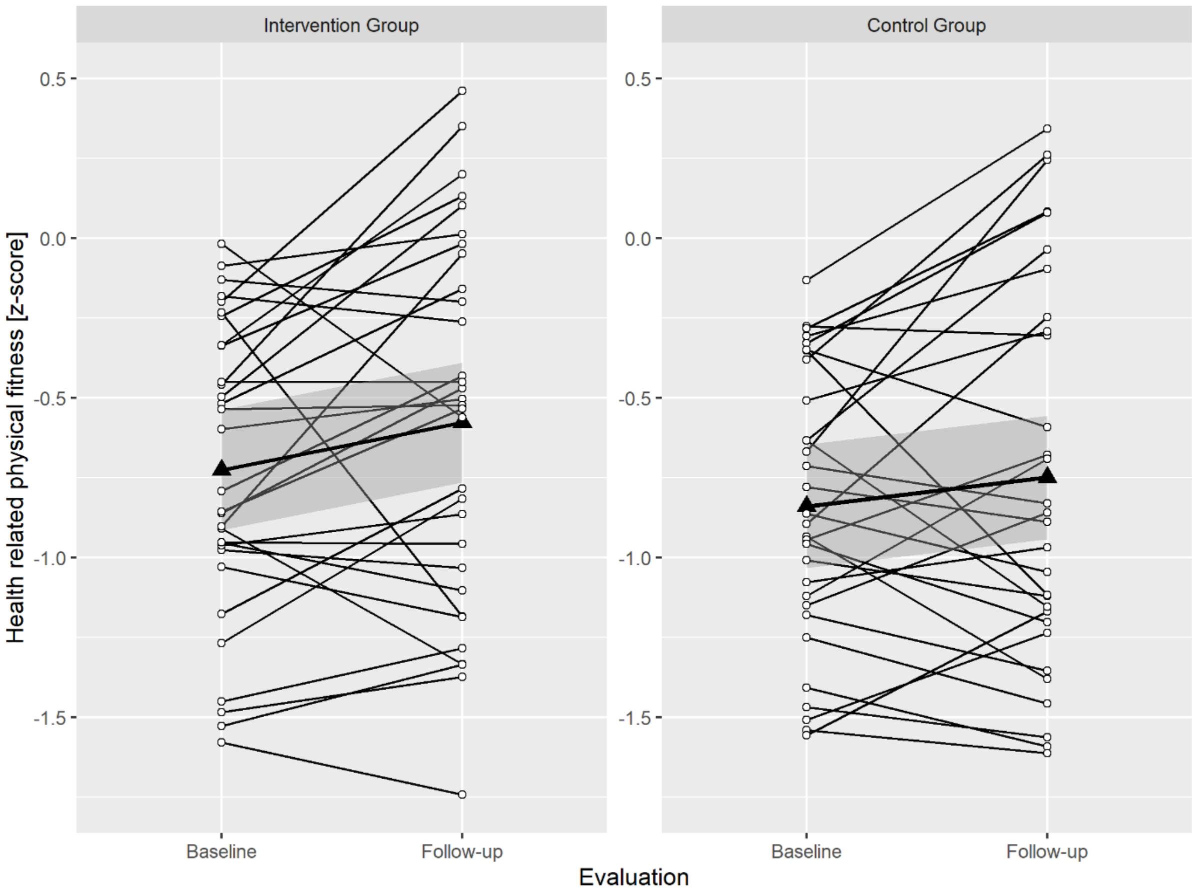

Figure 8 Within-subject development from Baseline to 24-weeks follow for HRPF.

HRPF: health-related physical fitness.

4 Summary and Clinical Perspective

The dissertation found that a 24-week web-based exercise intervention for children and adolescents with moderate or complex heart defects is feasible. In general, there were no adverse events due to the exercise intervention and the digital tracking tool could reliably document exercise adherence.
Despite individual flexibility to implement exercise training in daily life, the web-based exercise intervention could only improve the HRPF and HRQoL of some patients, while the majority lacked to improve.

In general, the findings suggest, that home-based exercise interventions can be useful and safe to improve functional outcomes such as exercise capacity or HRQoL for patients with CHD of all age groups. They should be an integral part of the cardiac rehabilitation of pediatric patients with CHD.[26,131,132,160,201] However, there is no clear consensus about what parameters are suitable for measuring the effects of rehabilitation.[131] While peak oxygen uptake is an important prognostic parameter in patients with CHD,[132] and therefore most often used in studies, other parameters such as muscle strength, body composition, or HRQoL could also influence patients with CHD. However, these are often rarely represented in studies.[131,160]
There are different cardiac rehabilitation formats available to these patients. Pilot projects such as the supervised children's sports group “Move-It” [202] offers permanent and regular supervised sports activities for children with chronic illnesses. However, the form and way in which a training program is offered can influence its sustainability.[26] Time-consuming extra effort or long distances to training locations can make participation considerably more difficult for patients particularly those living in rural areas.[131] As “Move-It” is an example of a program which is located in a city like Munich, people living in remote areas are unlikely to participate. Transferring the intervention to the patient’s home should be focused as a useful alternative to supervised groups such as “Move-It”.
In fact, especially in times of the Sars-Cov-2 pandemic, the importance of web-based exercise interventions becomes apparent. For example, during a pandemic, sports groups such as “Move-It” may have limited availability to vulnerable groups for infection control reasons. Despite carefully elaborated hygiene concepts, these programs have to be completely suspended during a lock-down anyway, which is why an important intervention is inevitably omitted for these patients.
However, being independent of location and in terms of temporal flexibility, does not automatically mean that the participants are therefore more adherent. Children and adolescents can have a very busy weekly schedule, which can be determined by various engagements. This can include anything from school obligations, such as homework or exams, to recreational activities, such as sports clubs, friends, and so on. Therefore, additional intervention necessarily competes directly with existing commitments.
The adherence to the web-based exercise intervention seemed to depend less on excessive demands than on the motivation of the patients and in part also on the involvement of parents in the training. Children whose parents regularly addressed training better adhered to the training.

Even though there have been:

1. Weekly email reminders in a motivating style for each participant.
2. Additional regular phone calls with parents/children, so that both parents and children experience a greater perception of the training.
3. Small incentives such as online games at the end of a session to increase and maintain intrinsic motivation for the training in the long run.

The adherence was not at an acceptable level. Even if the adherence rate seems to be quite low, a digital mapping tool included in the exercise platform was used, which should have detected the adherence of the participants quite accurately. Previous studies used conventional methods, such as paper and pen, and had to rely to the same extent on what their study participants documented independently.

Furthermore, the period in which the participants started the intervention might also have impacted their adherence. Overall, there could have been overlaps between the training intervention and the vacation period, when families began a journey. Even though the exercise intervention could in principle be conducted at any location with Internet access, it is not surprising that adherence dropped noticeably during a vacation.

Since the expression of the heart defects can be variable and individual, the trainability can also vary between the different categories of heart defects.[26] There might be abnormalities in other organ systems related to the heart defect, such as musculoskeletal abnormalities, e.g. connective tissue disorders or hypotonia.[131] Therefore our study protocol focused on a strengthening program to counteract these problems. Even if muscle strength was previously included in other studies, the majority of interventions for this patient group base on dynamic submaximal exercise training, preferring a steady-state design instead of interval training. This has the advantage that the training intensity can be determined at the beginning using peak oxygen uptake, peak heart rate, or the ventilatory threshold and can be readjusted during the training. However, strength is required in almost every activity of daily life, which is why the patient could benefit hereof. Despite the commonly applied 'no strength training dogma' in patients with CHD, strength training can induce significant changes.[26] Further there is an association between muscle strength and exercise tolerance,[203,204] which is why both aspects could be used in the rehabilitation of pediatric patients.

Even though we were guided by common interventions regarding our exercise duration of a single session as well as the overall program time, we can speculate that the standardized training protocol was not individual enough [131,197] for the relatively wide age range of our participants to show a training effect.

According to current experiences within this dissertation, web-based exercise interventions require a certain amount of framework for the participants. If possible, the intervention could be started in a supervised setting and then continued independently at home. The training contents should be age-appropriate and accordingly individually designed. In fact, digital group events that may take place on fixed weekdays could be considered. This would give each participant more than just a virtual training partner and could also benefit from positive interaction within the group.

A playful character could be more appealing to younger patients in particular and even more demanding on their motivation to stick with the intervention. In this respect including family members or peers such as friends or other children and adolescents, who have to cope with similar limitations, might play a key role to motivate for regular exercise and improve motor skills and quality of life for this patient group.

Regular training means at the same time a certain willingness and possibility to change behavior. The lack of effect of the exercise intervention raises the question of whether its development should have considered more behavior change theoretical frameworks such as Bandura's Social Cognitive Theory or Self-Determination Theory. In practical terms, the suggested gamification of the intervention, digital group events, or incentives such as weekly challenges are only some examples dealing with this topic. However, these should also be chosen with care, because depending on the child, too much challenge can quickly end in excessive demands.

To date, the application of a web-based exercise program is unique in the outpatient rehabilitation of pediatric patients with CHD. Its format was one of the first attempts with a lot of positive feedback from the children and their parents. And therefore efforts should be further intensified to develop eHealth approaches that can be used for the individualized rehabilitation of pediatric patients with CHD.

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6 Appendix

Exercise selection

I. Warm up		
No.	**Name**	**Category**
1	Walk on the spot	1
2	Knees lift crossed	
3	Light jogging	
4	Tapping	
5	Jumping jack sideways	
6	Jumping jack forwards	
7	Jumping jack combined	
8	Modified burpee	2
9	Mountain climber	
10	Tap the shoulder sideways	3
11	Tap the shoulder frontally	
12	Horizontal arm swinging forward/backward	
13	Circle the wrist arms abducted	4
14	Circle the wrist	

II. Main Part		
No	**Name**	**Category**
15	One-legged stand left	Coordination
16	One-legged stand right	
17	One-legged stand left (variation)	
18	One-legged stand right (variation)	
19/19a	One-legged stand left/right Elbow to opposite knee	
20	Back extender (diver)	Abdominal/Truncal/Back strenghtening
21	Back extender (bird)	
22	Crunches (straight)	
23	Crunches right/left (Beetle)	
24	Back swing	
25	Bridging backwards	
26	Reverse Plank	
27	All fours position backwards	
28	All fours position and push away from floor	
29	All fours position raise leg to the horizotal	
30	All fours position backwards, left knee and right elbow touch	
31	All fours position backwards, right knee and left elbow touch	
32	Plank forwards	
33	Plank sidewards right	
34	Plank sidewards left	
35	Cycling (supine poisition on the floor)	Strengthening Lower Extremity
36	Knee bend (back on the wall)	
37	Squats	
38	Squat Jumps	
39	Lunges forward	
40	Side lunge	
41	Push-ups knees bent	Streng-thening Upper Extremity
42	Push-ups	
43	Plank Switch	
44	Little buddha	

III. Cool Down		
No.	**Name**	**Category**
45	Stretching right wrist	Upper Extremity
46	Stretchingleft wrist	
47	Stretching Triceps	
48	Stretching Shoulder girdle	
49	Stretching shoulder girdle	
50	Stretching hamstrings	Lower Extremity
51	Stretching Qudriceps	
52	Stretching Adductors	
53	Supine lower trunk rotation left/right	

Exercises contributing to the units

Unit	I. Warm up				II. Main Part												III. Cool Down				Total
	Exercise				*Exercise*												*Exercise*				
1	1	13	8	10	15	16	35	36	20	21	24	28	30	31	41	43	45	46	50	53	20
2	2	14	9	11	15	16	39	40	21	20	22	27	33	34	43	41	48	47	51	53	20
3	3	13	8	12	15	16	35	37	20	21	25	29	30	31	41	43	49	47	52	53	20
4	4	14	9	10	15	16	39	40	21	20	24	28	33	34	43	41	45	46	50	53	20
5	5	13	8	11	17	18	35	38	20	21	22	27	30	31	44	41	48	47	51	53	20
6	6	14	9	12	17	18	39	40	21	20	25	29	33	34	43	41	49	47	52	53	20
7	7	13	8	10	17	18	35	36	20	21	26	28	30	31	44	41	45	46	50	53	20
8	2	14	9	11	17	18	39	40	21	20	23	27	33	34	43	41	48	47	51	53	20
9	3	13	8	12	19	19a	35	37	20	21	22	29	30	31	42	43	49	47	52	53	20
10	5	14	9	10	19	19a	39	40	21	20	26	28	33	34	43	41	45	46	50	53	20
11	6	13	8	11	19	19a	35	37	20	21	23	27	30	31	42	43	48	47	51	53	20
12	7	14	9	12	19	19a	39	40	21	20	22	29	33	34	43	41	49	47	52	53	20

Monthly schedule

Month		Week 1			Week 2			Week 3			Week 4			Total
1	Unit	5	11	7	4	9	10	7	10	3	4	12	6	**12**
2	Unit	6	8	7	4	5	3	10	1	11	3	4	7	**12**
3	Unit	12	5	9	8	7	11	7	12	5	4	10	11	**12**
4	Unit	1	12	6	11	5	10	9	11	9	3	2	3	**12**
5	Unit	12	2	10	7	8	4	10	11	9	2	5	12	**12**
6	Unit	7	5	8	8	4	10	7	6	7	3	4	2	**12**

Journal Permissions

Study I

Meyer M, Brudy L, García-Cuenllas Alvarez L, Hager A, Oberhoffer R, Ewert P, Müller J; Current state of home-based exercise interventions in patients with congenital heart disease: a systematic review Heart 2020;106:333-341. DOI: 10.1136/heartjnl-2019-315680

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