Physical Activity

in Patients with Congenital Heart Disease

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Physical Activity in Patients with Congenital Heart Disease

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»La semplicità è l’ultima sofisticazione«

»Einfachheit ist die höchste Stufe der Vollendung«

Leonardo DaVinci

Summary

Improvements in prenatal diagnostics and surgical techniques have tremendously increased live expectancy in patients with congenital heart disease. Thus, the number of patients living with congenital heart disease is continuously growing and the prevention of secondary diseases has become the focus of medical aftercare. Encouragement towards a physically active lifestyle is at the core of this preventative approach.

Whether these encouragements towards more physical activity are landing on fertile ground are at the center of the research of this dissertation. A systematic literature review found that the overall study quality of research on the topic was fair at best and that the included studies lack comparability due to methodological differences. In three cross-sectional studies with wearable physical activity tracking devices on a self-recruited cohort of young children, adolescents, and adults with congenital heart disease, it was found that the majority of children and adolescents are sufficiently active. However, a physically active lifestyle needs to be promoted in young patients who are overweight, obese, or of complex defect severity. Furthermore, the more active young patients are, the higher their likelihood to be happier in the form of better health-related quality of life. Adult patients with congenital heart disease on the other hand lacked intensity in their daily movement and need to be encouraged to move more as they are failing to reach general physical activity recommendations as well as physical activity levels of their healthy peers. This is especially crucial in the context of lower exercise capacity in this cohort and an aging patient population. And lastly, subjective physical activity estimation of young patients is fairly correct in about half of all children while the large majority of adult patients overestimates how active they really are. The older the patients with CHD, the less active they are and the less accurate their subjective estimation of their PA behavior.

The results of this dissertation raise further research perspectives. Two examples might be how physical activity can be promoted in inactive patients, and how young active patients can be kept active into adulthood. Furthermore, exploring the triangular relationship of daily physical activity, exercise capacity, and possible cardiac anxiety, as well as determining the association between daily physical activity and arterial stiffness across all ages of patients with congenital heart disease are crucial next steps. Lastly, patients with congenital heart disease who are currently not tied to specialized healthcare structures should not be forgotten about.

Zusammenfassung

Verbesserungen in pränataler Diagnostik und operativer Versorgung haben die Lebenserwartung bei Patienten mit angeborenen Herzerkrankungen enorm erhöht. Daher steigt die Zahl der Patienten mit angeborenem Herzfehler stetig. Dabei ist die Prävention von Sekundärkrankheiten zum Schwerpunkt der medizinischen Nachsorge geworden. Die Förderung eines körperlich aktiven Lebensstils steht im Mittelpunkt dieses präventiven Ansatzes.

In dieser Dissertation steht die Frage, ob diese Förderung zu mehr körperlicher Aktivität auf fruchtbarem Boden gelandet ist, im Mittelpunkt der zugrunde liegenden Forschung. Eine systematische Literaturrecherche ergab, dass die Gesamtstudienqualität der Forschung zu diesem Thema bestenfalls durchschnittlich war und dass die bisherigen Studienergebnisse aufgrund methodischer Unterschiede nicht vergleichbar sind In drei Querschnittsstudien mit Fitness-Trackern zur Messung der körperlichen Aktivität von kleinen Kindern, Jugendlichen und Erwachsenen mit angeborenem Herzfehler wurde festgestellt, dass die Mehrheit der Kinder und Jugendlichen ausreichend aktiv ist. Ein körperlich aktiver Lebensstil muss jedoch bei jungen Patienten gefördert werden, die übergewichtig oder fettleibig sind, oder an einem komplexen Herzfehler leiden. Darüber hinaus wurde festgestellt, je aktiver junge Patienten sind, desto höher ist ihre Wahrscheinlichkeit in Form einer besseren gesundheitsbezogenen Lebensqualität glücklicher zu sein. Erwachsene Patienten mit angeborenen Herzerkrankungen hingegen hatten keine Intensität in ihrer täglichen Bewegung und müssen ermutigt werden, sich mehr zu bewegen, da sie die allgemeinen Empfehlungen für körperliche Aktivität sowie das Niveau ihrer gesunden Altersgenossen nicht erreichen. Dies ist besonders wichtig im Zusammenhang mit einer geringeren körperlichen Leistungsfähigkeit in dieser Kohorte sowie einer alternden Patientenpopulation. Und schließlich ist die subjektive Schätzung der körperlichen Aktivität junger Patienten bei etwa der Hälfte aller Kinder korrekt, während die große Mehrheit der erwachsenen Patienten überschätzt, wie aktiv sie wirklich sind. Je älter die Patienten mit angeborenem Herzfehler sind, desto weniger aktiv sind sie und desto weniger genau ist die subjektive Einschätzung ihrer körperlichen Aktivität.

Die Ergebnisse dieser Dissertation eröffnen weitere Forschungsperspektiven. Wie kann beispielsweise körperliche Aktivität bei inaktiven Patienten gefördert werden und wie können junge aktive Patienten bis ins Erwachsenenalter aktiv gehalten werden? Darüber hinaus sind die Untersuchung der Dreiecksbeziehung zwischen täglicher körperlicher Aktivität, körperliche Leistungsfähigkeit und möglicher Herzangst, sowie die Bestimmung

des Zusammenhangs zwischen täglicher körperlicher Aktivität und arterieller Gefäßsteifigkeit über alle Altersgruppen von Patienten mit angeborenen Herzerkrankungen hinweg entscheidende nächste Schritte. Zuletzt sollten Patienten mit angeborenem Herzfehler, die derzeit nicht an spezialisierte Gesundheitsstrukturen gebunden sind, nicht vergessen werden.

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Abbreviations

ACC	American College of Cardiology
AS	Aortic Stenosis
ASD	Atrial Septal Defect
AVSD	Atrioventricular Septal Defect
CHD	Congenital heart disease
CoA	Coarctation of the Aorta
HLHS	Hypoplastic Left Heart Syndrome
MET	Metabolic Equivalent
HRQoL	Health-Related Quality of Life
EBS	Ebstein's Anomaly
MVPA	Moderate-to-vigorous Physical Activity
PA	Physical Activity
PDA	Patent Ductus Arteriosus
PS	Pulmonic Stenosis
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
TAC	Truncus Arteriosus Communis
TAPVC	Total Anomalous Pulmonary Venous Connection
TGA	Transposition of the Great Arteries
ToF	Tetralogy of Fallot
UVH	Univentricular Heart
VO_2	Oxygen Consumption
VSD	Ventricular Septal Defect
WHO	World Health Organization

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1 Background

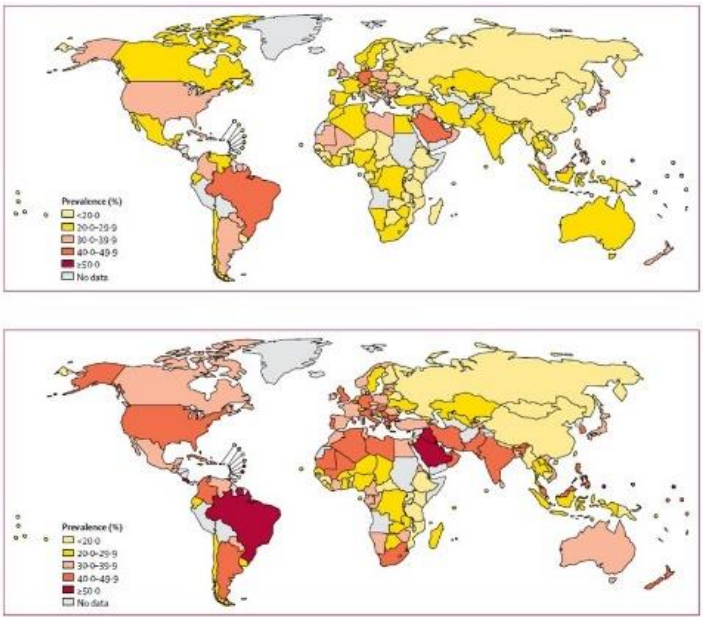
1.1 General Introduction

At time of writing this dissertation, the world has been kept at suspense by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which was declared a global pandemic in March 2020 by the World Health Organization (WHO)[1]. For quite some longer time, another, more silent pandemic has gained momentum worldwide: physical inactivity [2]. Just behind hypertension, tobacco usage, and high blood-glucose, physical inactivity is the fourth leading cause for global mortality, and a key risk factor for non-communicable diseases such as cardiovascular diseases, cancer and diabetes [3]. However, not only diseases and early deaths are at the horizon of physical inactivity [4]. It also imposes a major economic burden in terms of productivity losses and health care expenditures and has a negative impact on the environment, community well-being and quality of life[5].

As of data from 2016, the world is currently looking at physical inactivity in 27.5% of its entire adult population, with some countries going as high as 43%. That is over 1.8 billion people worldwide. When compared by gross-national-product, high-income countries tend to have the highest proportion of physically inactive people [6]. In other words, the more developed a country is, the less likely its inhabitants are to achieve sufficient levels of physical activity (PA). In that way, they also become more susceptible to suffer from non-communicable diseases or further comorbidities such as Type-II-Diabetes, cardiovascular disease, or cancer. As a result, physically inactive people become chronically ill [3]. Figure 1 – adapted from Guthold et al. [6] - illustrates the extent of this global physical inactivity pandemic with data from 2016. Put simply, wherever data is available, people are not sufficiently active.

The above-mentioned context deals mostly with acquired chronic illnesses that people develop due to physical inactivity. Congenital heart disease (CHD), on the other hand, is a term referring to structural defects of the heart existing since birth. With a prevalence of 1.8 per 100 live births, they are the most common human congenital anomaly [7].

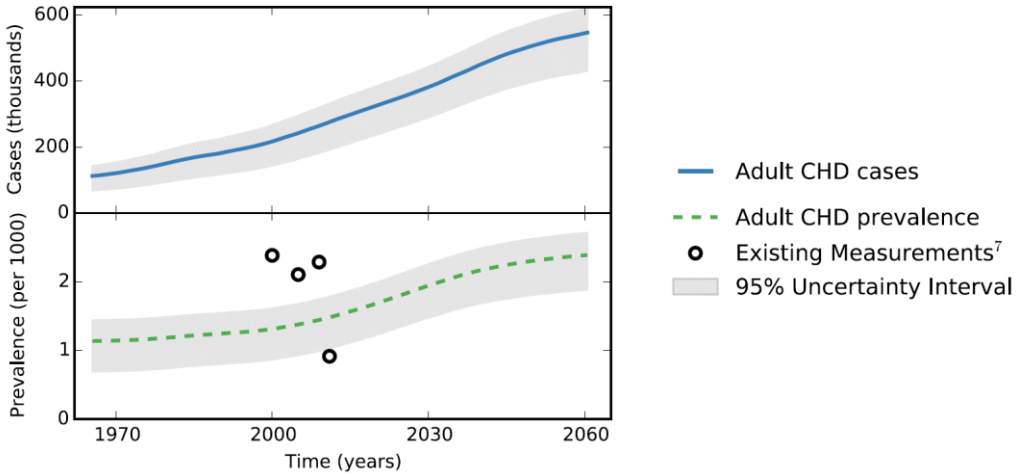
Figure 1: Worldwide prevalence of physical inactivity in men (top) and women (bottom)



Adapted from Guthold et al. [6]

Improvements in prenatal diagnostics and surgical techniques have tremendously increased live expectancy. Therefore, in the developed world, almost every infant born with CHD can expect to reach adulthood. In 2017, roughly 12 million people worldwide lived with CHD [8] and this number is expected to grow continuously over the next decades [9]. Figure 2 - adapted from Benzinger et al. [9] – illustrates this projected growth of the adult CHD population. As a result, management of disease course and especially the prevention of secondary diseases has become the focal point of medical aftercare in this patient population [10].

Figure 2: Estimated Number of Adults with Congenital Heart Disease 1965 to 2060



Adapted from Benziger et al. [9]

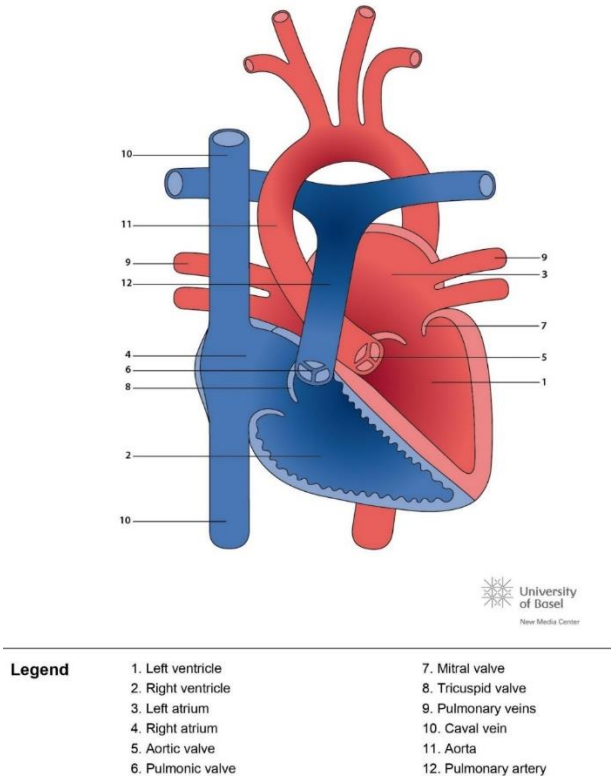
Aside from regular routine medical consultation, the encouragement towards a physically active lifestyle and regular sports participation are at the core of this preventative approach. The goal thereby is to ensure healthy development, support cardiovascular health and prevent the development of chronic diseases. However, in the past patients with CHD have generally been described to be relatively sedentary and were restricted from exercising, even though it is now known that exercise and PA vastly improve medical outcome and long-term prognosis of these patients [11]. In fact, exercise capacity is a long-known predictor of mortality and morbidity and shown to be lower in patients with CHD than in otherwise healthy. In other words, the fitter a patient with CHD is, the more likely his or her survival at any age [12]. And the more physically active a person the higher his or her fitness at any age [13,14].

Now taking these insights about a global physical inactivity pandemic and a growing chronically ill population together one might conclude this to be a recipe for disaster. Before going into detail about how active patients with CHD really are, a few key concepts around CHD, PA and its measurement need to be further explored.

1.2 Congenital Heart Defects

The human heart is an astonishing organ. In the embryonic phase of the developing fetus, its heart starts beating around week five to six of gestation. At this earliest stage, the heart simply consists of two tubes which have merged in the middle thereby forming a trunk with four tubes diverging from it. Within only five to six more weeks, this rudimentary heart changes rapidly, developing ventricles, atria, valves, as well as the aorta and pulmonary vein. By the 10th week of pregnancy, the fetal heart has fully developed and – with current live expectancies – does not stop beating until more than 80 years later. Figure 3 depicts the healthy, fully developed heart. Blood flows through the healthy heart in four steps: Oxygen-poor blood enters the right atrium from the body and circulates it through the tricuspid valve into the right ventricle which then further pumps the blood through the pulmonary valve into the lungs. The left atrium receives the now oxygenated blood from the lungs and circulates it through the mitral valve into the left ventricle. From there, the oxygen-rich body flows through the aortic valve into the rest of the body.

Figure 3: The healthy heart



Usually, this embryonic development is a rather structured, well developed process, which runs smoothly without any problems in 99% of all pregnancies. However, in the

remaining 1% this process deviates from the norm which then can lead to structural malformations of the great vessels. As a result, CHD in different forms and combinations with diverse impacts on functionality can occur [15].

Reasons for CHD are manifold, yet no clear cause has been identified. It can form due to chromosomal abnormalities, genetic predispositions, or disruptions during pregnancy such as abuse of certain medications, drugs, or alcohol. Furthermore, infections or chronic diseases of the mother can also have a negative impact on the development of fetal heart defects [16].

As previously mentioned, CHD is the most common human congenital anomaly. The proportion of people living with CHD at a particular time period, the prevalence, has increased steadily by 18.7% from 1990 to 2017 due to continuous improvements of prenatal diagnostics and surgical correction techniques [7]. The incidence depends largely on the definitions of inclusion criteria and the specific disorders examined. Very generally, every 100th baby is born with CHD [17]. The specific rate in Germany was 107.6 per 10.000 live births in 2007 [18]. Table 1 provides further prevalence according to CHD types.

The extent of these malformations depends on whether they occur isolated as a single defect or in combination of several defects. Each CHD can have different impacts on functional status of the heart. They can thereby be separated into simple, moderate and complex severity. The American College of Cardiology (ACC) has published commonly used guidelines according to which all CHD are assigned a specific severity class and which provides further details [19]. The large majority of all defects in Germany are of simple severity (60.6%). Moderate (27.4%) and complex (12.0%) lesions occur less often. Very broadly, the spectrum ranges from simple defects with no need for medical aftercare or interventions, to very complex CHD that require lifelong medical aftercare and surgical interventions early on. While these criteria are the underlying definitions for all CHD throughout the project of this dissertation, for a better understanding further differentiation of CHD will be described below.

CHD can also be classified according to the *New York Heart Association* (NYHA) criteria which rate the extent of heart failure into four different subcategories according to limitations and symptoms [20]. However, NYHA class is focused on functionality instead of lesions which is why the majority of this dissertation focuses on the ACC criteria [19].

Each different type of CHD can have a different effect on the level of oxygen in the blood, the oxygen saturation. If this level is too low, the blood cannot supply enough oxygen to

the tissues and organs of the body thereby possibly compromising their function. Normal arterial oxygen saturation is between 95 to 100% at rest. In the context of CHD, the oxygen saturation levels at rest result in a distinction between cyanotic (oxygen saturation <85%) and acyanotic CHD [21]

The specific location of the defect provides another possibility of distinction between CHD. Throughout this dissertation six major subgroups based on the spot of the malformation are introduced and considered: Left Heart Obstruction, Isolated Shunts, Right Heart Obstruction, Transposition of the Great Arteries, Hypoplastic Left Heart Syndrome or Univentricular Heart, and Miscellaneous defects.

The descriptions of the specific defects in these subgroups were retrieved from »*Kompendium angeborene Herzfehler bei Kindern – Diagnose und Behandlung*« [16], which also provides more in-depth elaborations. The accompanying illustrations are from http://www.chd-diagrams.com. These illustrations are licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License by the New Media Center of the University of Basel.

Table 1: Prevalence of Congenital Heart Disease in Germany

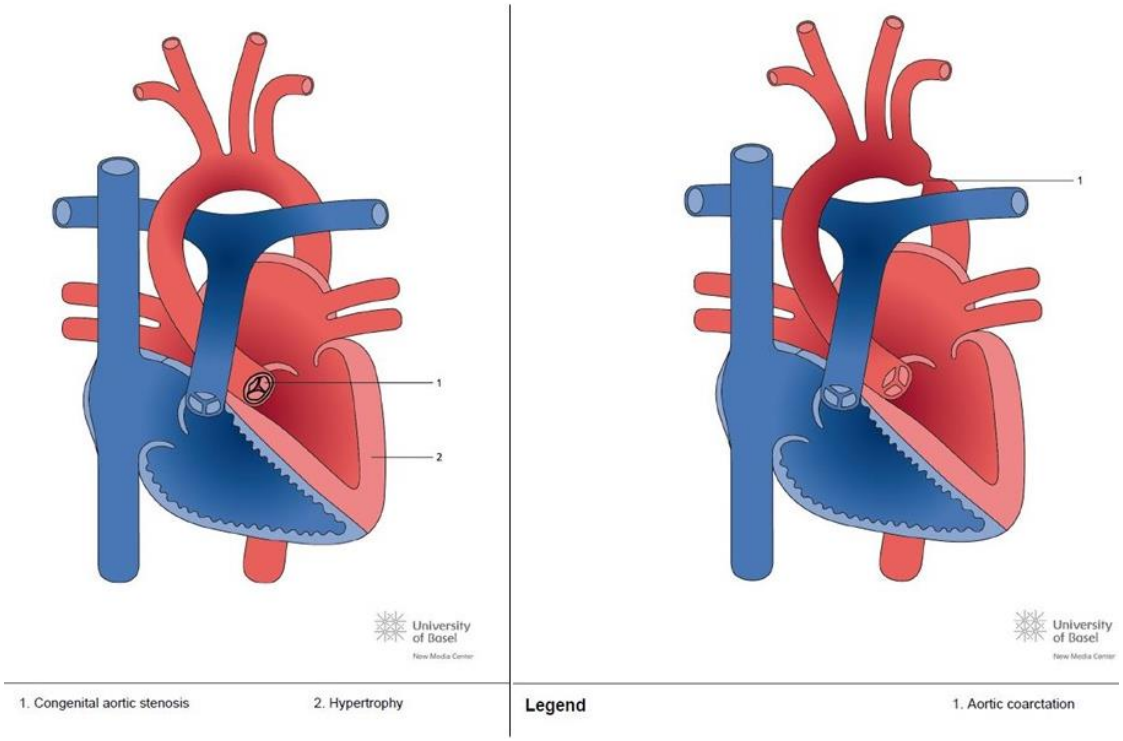
CHD	Prevalence per 10.000 live births[18]	Percentage of live births	Subgroups
Aortic Stenosis	2.4	0.02%	Left Heart Obstruction
Coarctation of the Aorta	3.9	0.04%	Left Heart Obstruction
Atrial Septal Defect	18.3	0.18%	Isolated Shunts
Ventricular Septal Defect	52.7	0.53%	Isolated Shunts
Atrioventricular Septal Defect	2.7	0.03%	Isolated Shunts
Pulmonary Stenosis	5.6	0.06%	Right Heart Obstruction
Tetralogy of Fallot	2.7	0.03%	Right Heart Obstruction
Transposition of the Great Arteries	2.7	0.03%	TGA
Univentricular Heart	3.0	0.03%	UVH

Left Heart Obstruction

Aortic stenosis (AS) describes the narrowing of the aortic valve which is responsible for controlling the blood flow from the left ventricle into the aorta. The valve does not open or close properly thereby reducing blood flow from the heart into the aorta and the rest of the body. As a consequence, the ventriculus sinister outlet is narrowed, pressure inside the heart increases and left ventricular hypertrophy may result.

A narrowing of the aorta at the ligamentum arteriosum insertion is commonly labeled as *Coarctation of the Aorta* (CoA). Reduced blood flow into the descending aorta and increased blood pressure may result in left ventricular hypertrophy.

Figure 4: Aortic Stenosis (left) and Coarctation of the Aorta (right)

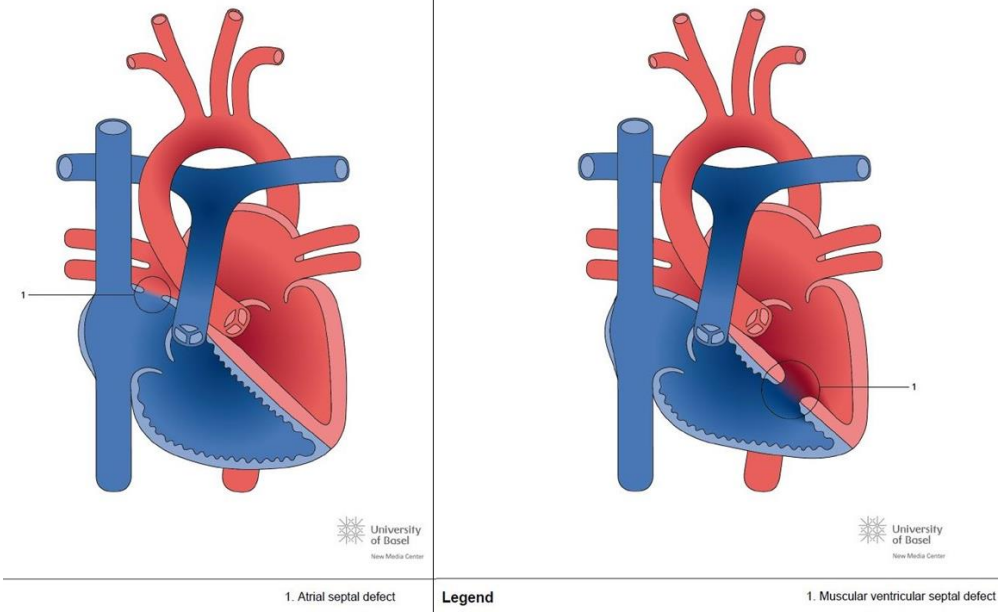


Isolated Shunts

Defects in the form of holes can occur between the atria or the ventricles. Such defects lead to different pressures in both chambers. Oxygen-rich and oxygen-poor blood from both sides of the heart mix, which is usually referred to as a shunt. This volume overload may lead to hypertrophy of the chambers, pressure overload results and oxygen saturation may be lower. While smaller defects are sometimes not detected until later in life or often eventually close by themselves, larger defects need to be closed through heart catheter surgical intervention. All shunts result in volume overload or pressure overload and can lead to right heart enlargement and pressure increase in the right ventricle. In colloquial terms, this defect group may be referred to a hole in the heart.

A defect between the atria is an *Atrial Septal Defect* (ASD), while a *Ventricular Septal Defect* (VSD) occurs a little lower between the two ventricles of the heart. In both cases oxygen-rich blood leaks into the oxygen-poor atria or ventricle respectively.

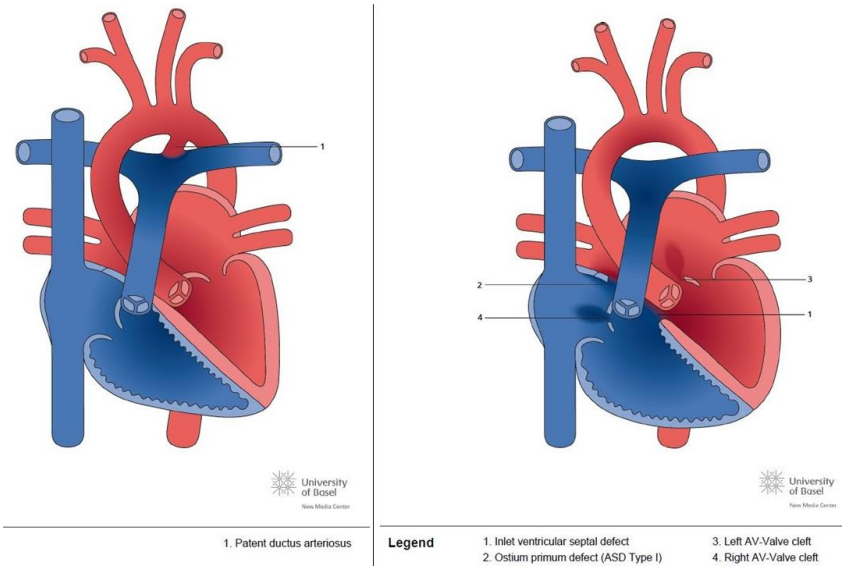
Figure 5: Atrial Septal Defect (left) and Ventricular Septal Defect (right)



A combination of both ASD and VSD can also occur, referred to as an *Atrioventricular Septal Defect* (AVSD), either partially or in a complete version. Again, oxygen-rich blood from the lungs mixes with oxygen-poor blood from the body, resulting in an increased workload for the heart possibly leading to congestive heart failure.

A last defect in the subgroup of isolated shunts is the *Patent Ductus Arteriosus* (PDA). In the fetal heart, the ductus arteriosus is a vessel connecting the pulmonary artery and the aorta. This connection is needed as the lungs are not working normally in the womb, and usually closes within the first few seconds after birth. If this connection does not close it is referred to as a PDA.

Figure 6 : Patent Ductus Arteriosus (left) and Atrioventricular Septal Defect (right)



Right Heart Obstruction

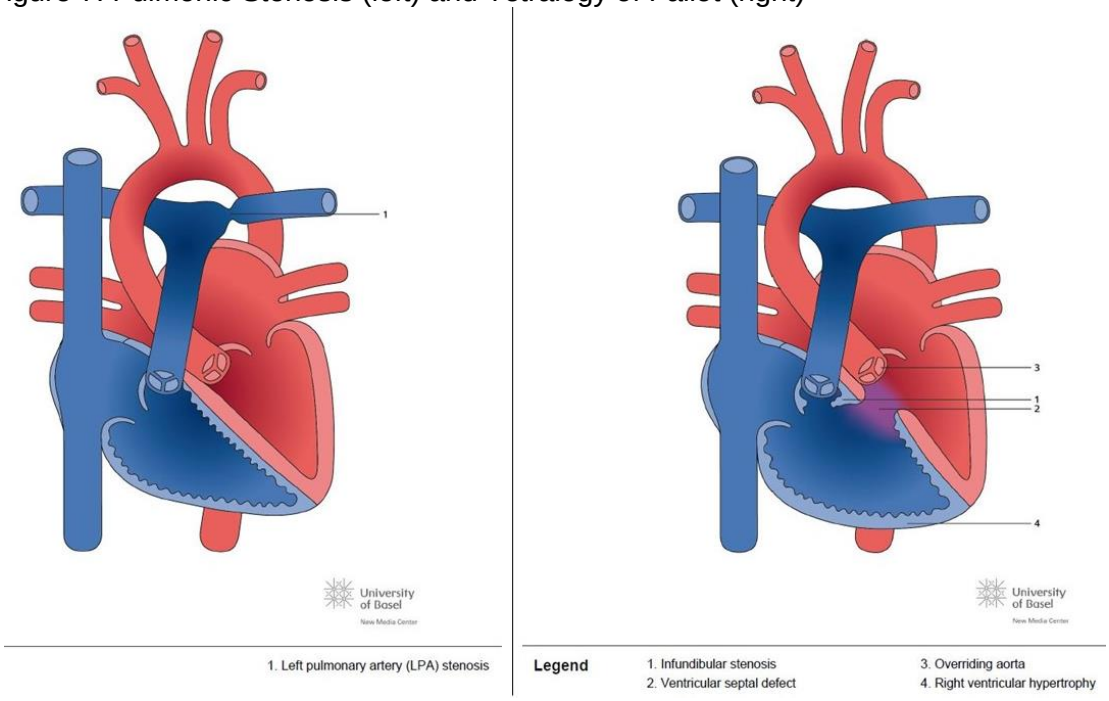
Sometimes the pulmonary artery or the pulmonary valve can thicken or be deformed resulting in a narrowed outlet obstructing blood flow to the lungs. This defect is referred to as *Pulmonic Stenosis* (PS). Normal blood flow is hampered resulting in right ventricular hypertrophy due to the increased workload on the heart needed to pump the blood into the lung.

Very rarely, several defects can combine. A *Tetralogy of Fallot* (ToF) is such a combination of four individual defects:

- PS
- VSD
- Overriding Aorta - a defect in which the aorta is positioned directly over the VSD instead of over the left ventricle. Thereby, the aorta receives blood from the right ventricle with limited oxygen supply to the tissues.
- Right Ventricular Hypertrophy - abnormal enlargement of the cardiac muscle surrounding the right ventricle.

It may also be defined by a malalignment VSD with an overriding aorta, where the PS and the right ventricular hypertrophy are simply the result of these conditions. Patients with ToF need surgical interventions within the first year of life to ensure survival. These patients, even later in life, may sometimes present with a blueish skin color, a sign of low oxygen saturation, or cyanosis.

Figure 7: Pulmonic Stenosis (left) and Tetralogy of Fallot (right)

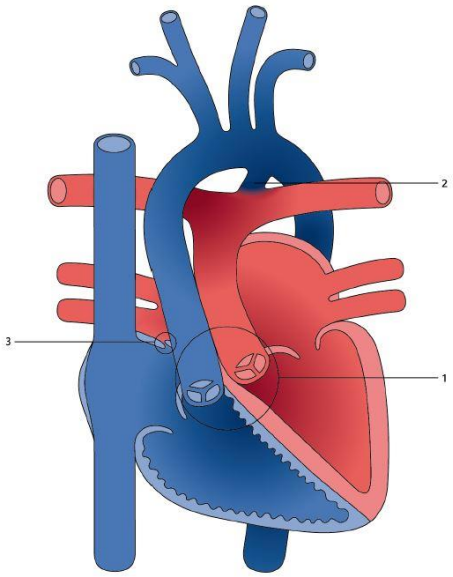


Transposition of the Great Arteries

Transposition of the Great Arteries (TGA) describes a condition in which the pulmonary artery and the aorta are reversed, thereby creating two separate circulations without oxygen-rich blood circulating through the body. In other words, the pulmonary artery emerges from the left, and the aorta from the right which is opposite to a healthy heart. In a healthy heart, the large arteries are connected to the heart in exactly the opposite way, so that the two circulations can run one after the other.

These patients require surgical intervention to ensure survival. Several procedures exist with the two most common atrial switch procedures named after the first surgeons who performed these rerouting operations independent of each other: Senning and Mustard. These operations have become more and more obsolete nowadays and have been replaced with arterial switch operations as these provide a better long-term outcome. The operation is usually carried out in the first few days or weeks of life with use of the heart-lung machine. Within the procedure, the aorta is detached from the right atrium and connected to the left atrium; the pulmonary artery is detached from the left atrium and tied to the right atrium. After this correction, blood flow is anatomically correct again, i.e. the left ventricle pumps into the aorta, and the right ventricle into the pulmonary arteries. Interestingly, the new aortic valve is actually the anatomical pulmonary valve, and conversely the new pulmonary valve is the original aortic valve.

Figure 8 : Transposition of the Great Arteries



Legend 1. D-Transposition of the great arteries 2. Persistent ductus arteriosus 3. Patent foramen ovale

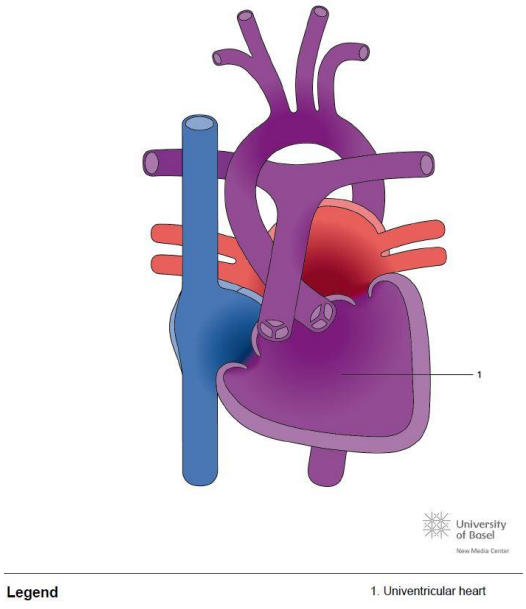
Hypoplastic Left Heart Syndrome and Univentricular Heart

This subgroup entails all defects with an underdeveloped left chamber, and the functioning of only one ventricle. Such defects are the Univentricular Heart (UVH), the Hypoplastic Left Heart Syndrome (HLHS), or the missing of a valve such as the pulmonary or tricuspid atresia. Characteristical for the HLHS is the underdevelopment of the aorta, valva aortae, ventriculus sinister and valva atrioventricularis sinistra. Due to the complexity of this defect, the therapy consists of several palliative surgical interventions carried out in three stages:

- 1st intervention: aortopulmonary shunt and pulmonary artery banding relatively soon after birth
- 2nd procedure: Glenn's anastomosis 4-12 months after birth
- 3rd procedure: Fontan Operation 24-60 months after birth

Through surgical interventions two separate blood circuits need to be created. The processes entail a total cavopulmonary connection (TCPC) which results in the so-called Fontan Circulation. Again, patients in this subgroup suffer from shunts and lower blood oxygenation. This subgroup represents one of the most complex malformations.

Figure 9: The Univentricular Heart



Miscellaneous

A few further, even rarer defects are summed up in this category (Table 2). Such rare defects can be the Ebstein Anomaly (EBS), the Truncus Arteriosus Communis (TAC), or

the Total Anomalous Pulmonary Venous Connection (TAPVC) which often appear in combination with other defects.

Table 2: Miscellaneous Congenital Heart Defects

CHD	Prevalence per 10.000 live births in Germany[18]	Characteristics
EBS	0.4	Deformed and displaced tricuspid valve downwards into the right ventricle leading to tricuspid regurgitation and resulting right heart failure.
TAC	0.5	The pulmonary artery is either missing or very small and arises as an arterial trunk from the aorta. Lower oxygen saturation results from shunt.
TAPVC	0.6	Mispositioned pulmonary veins into the right atrium instead of the left. Lower oxygen saturation results from shunt.

EBS: Ebstein Anomaly, TAC: Truncus Arteriosus Communis, TAPVC: Total Anomalous Pulmonary Venous Connection

Some CHD do require surgery or catheterization, some do not. Eventually, specific classification to *any* of the groups and severity classes depends on individual medical history and functional status. Furthermore, the requirement of implantations of artificial valves also plays a role on group allocation.

1.3 Physical Activity

PA is defined as »*any bodily movement produced by skeletal muscles that requires energy expenditure*« [22]. It is a fundamental concept as in order to sustain life everyone performs some sort of PA. The extent to which degree a person is physically active varies considerably and depends on time and individual choice amongst others. PA can either be structured, such as planned exercise with the goal of promoting health and fitness, or incidental, which is not planned and usually the result of daily activities.

PA and especially its measurement cannot be fully understood without a short excursion on energy expenditure. Energy expenditure is *»the amount of energy an individual uses to maintain essential body functions«* whether it be breathing, blood circulation, food digestion or any activity such as exercise [23].

Even though the concepts have a number of commonalities, PA should not be confused with *exercise*, which is a subcategory of physical activity that is planned, structured, repetitive, and aims to improve or maintain one or more components of physical fitness. In other words, all exercise an individual does is PA, but not all PA is exercise. *Physical fitness* is another concept closely related to PA. It is a set of attributes of a person and defined as »*the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies*« [24]. It is, however, beyond the scope of this dissertation.
PA is a complex behavior to analyze. Therefore, the four dimensions *frequency, intensity*, *type*, and *time* need to be considered before going into more detail, sometimes also referred to as *FITT criteria* (Table 3) [25].

Table 3: FITT criteria

Frequency	number of sessions per specific timeframe such as day, week, month or year
Intensity	measure of metabolic demand of an activity
Time	Specific time spent in a physically active behavior
Type	Specific activity performed, for example walking, running, cycling, gardening.

While *frequency* and *time* are self-explanatory, *type* and *intensity* need further elaborations. *Type* - sometimes also referred to as *mode* - of PA can in more detail be described in the context of its demands either physiologically such as aerobic or anaerobic activity, or biomechanically such as resistance or strength training, and balance or stability training.

Intensity as a measure of the »metabolic demand of an activity« can be further understood in the context of energy expenditure. PA always requires energy to be expended. The higher the intensity, the higher the rate of energy expenditure and its impact on the metabolism. PA intensity can be rated and assessed subjectively, such as an individual stating the level of perceived exertion, or objectively, through a measure of the heart rate or oxygen consumption. More generally, and more importantly for the context of this dissertation: PA intensity is usually rated as moderate, vigorous or a combination of the two levels.

To further grasp PA intensity and its ratings, the metabolic equivalent of task (MET) as the common unit to quantify PA intensity levels is important to understand. One MET refers to the resting energy expenditure while sitting around quietly and is defined as in the consumption of 3.5 ml of oxygen per kilogram body mass per minute. Intensity levels are then described in multiples of one MET and with this concept a transfer to the commonly known terms *light*, *moderate* and *vigorous* is possible [25]. PA intensities are always considered in multiples of sitting quietly, or one MET (Table 4).

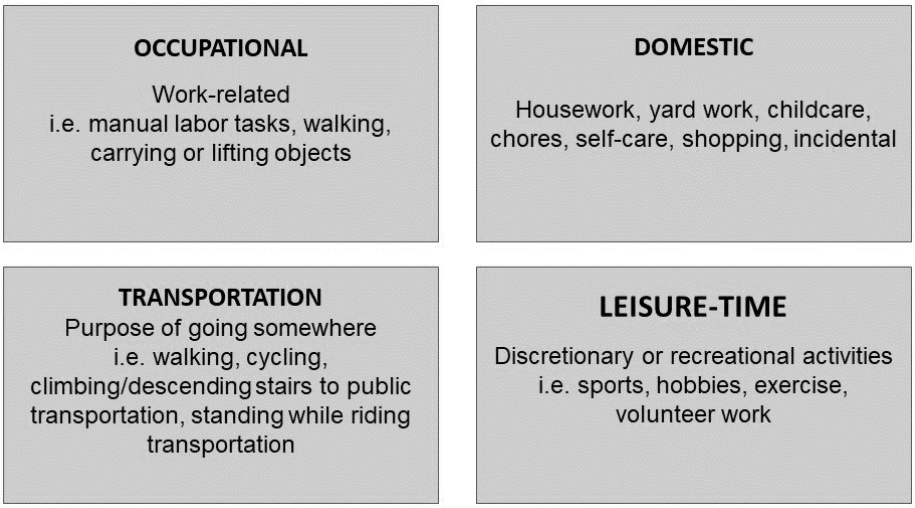
Table 4: Physical Activity Intensities

Light	All activities requiring <3.0 METs i.e. walking slowly, playing an instrument, or doing light work standing
Moderate	All activities requiring 3.0-6.0 METs i.e. brisk walking, light cycling or recreational badminton
Vigorous	All activities requiring >6.0 METs i.e. jogging, fast cycling, basketball or soccer game

While this is the commonly employed measure of PA and exercise intensity, it does come with a substantial flaw we must be aware of. While a classification such as light, moderate, and vigorous describes PA in absolute terms, namely by the external work performed, PA is also always relative to an individual's level of fitness. For example, brisk walking is usually defined as moderate PA requiring 3.0 to 6.0 METs. However, if we consider the physical fitness of 25-year old-marathon runner and 95-year-old lady in comparison it becomes apparent that a brisk walk would be a very light activity for the former, and a quite vigorous for the latter [25]. To combat this flaw, energy expenditure during PA (and thereby intensity levels of exercises) is also sometimes quantified in relation to the body mass as kilocalories per kilogram of body mass per minute. However, this expression as well as the kilocalorie as a unit of measurement is beyond the scope of this dissertation and can be accessed elsewhere [25].

Besides its dimensions, the categorization of PA by domain in which it occurs is also a central concept in the description and the assessment of it [22]. Figure 10 depicts these domains.

Figure 10: Physical Activity Domains

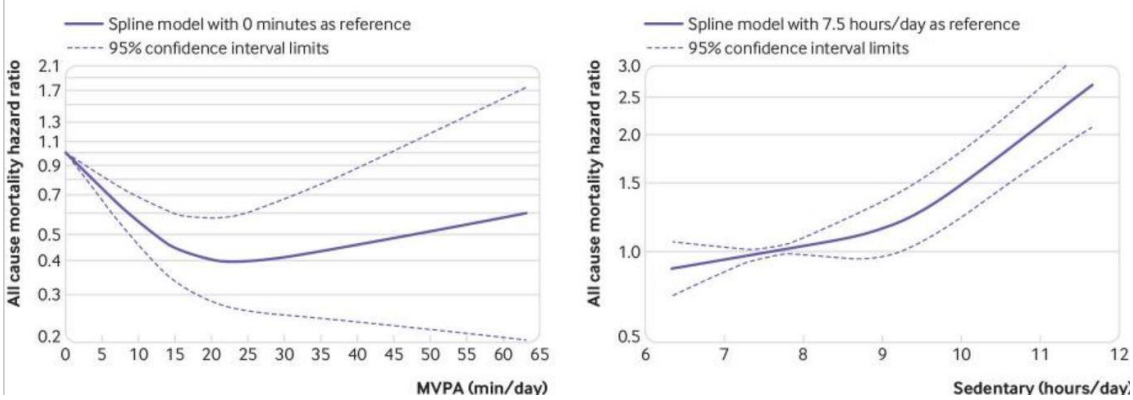


Why is Physical Activity so important?

Independent of the categorization and realm of PA, it is important to consider that beyond exercise any physically active behavior, whether it be during leisure time, as part of a person's work, or as means of transportation, has health benefits [26]. But why exactly is regular PA so important?

As mentioned earlier, physical inactivity is the fourth leading risk factor for global mortality. Together with an unhealthy diet, and harmful use of tobacco or alcohol, physical inactivity is a key modifiable risk factor for non-communicable diseases leading to four major physiological and metabolic changes in the human body: overweight/ obesity, increased blood pressure (hypertension), excessive amounts of blood-glucose (hyperglycemia), and elevated levels of blood lipids such as fat, cholesterol or triglycerides (hyperlipidemia). According to the WHO people who do not reach sufficient PA levels have a risk of premature death 20% to 30% higher than people who do. Higher levels of PA at any intensity, and lower levels of time spent sedentary, are associated with substantially reduced risk for premature mortality [27]. Figure 11 – modified from Ekelund et al. [27] - illustrates this dose-response relationship between PA and sedentary behavior per day and all-cause mortality.

Figure 11: Dose-response relationship of all-cause mortality to moderate-to-vigorous physical activity (left) and sedentary time (right)



Modified from Ekelund et al. [27]

In fact, more than five million deaths could be prevented every year if people all around the globe were more active. And even though this problem is being tackled through operational policies in more than half of all member states of the WHO with the goal of reducing physical inactivity by 10% in 2025, there have been no global improvements in PA levels since 2001 [28]. Motorized means of transportation, occupational transformations to a more white-collar workforce, and increased usage of screens for education, work, and recreation lead to people's lives becoming even more sedentary [28]. The results of these increasingly sedentary lifestyles are at first weight gain, poor sleep, and a reduction in cardiometabolic health and fitness which then transform into increased incidence of non-communicable diseases such as cancer, type-2-diabetes, or cardiovascular disease [3]. On a global scale in 2016, a staggering 81% of adolescents and more than a quarter of the world's adult population were not sufficiently active enough [28]. The socioeconomic impact of global inactivity is immense. Even though difficult to assess, the annual direct health-care costs were estimated to range from US$28.4 to $334.4 per person in Australia [29]or the UK [30] and estimated indirect annual costs from $154.7 to $418.9 per head in Canada [31] and the USA [32] in the early 2000s and 2010s. Rapid economic development and resulting social changes in Latin America [33] or fast urbanization leading to changing means of transportation in Asia [34] further contribute to the decline of PA all around the world. Physical inactivity therefore is, in fact, a global pandemic [2].

In order to address this pandemic increasing and sustaining PA are of utmost significance in disease prevention and health promotion and can be addressed from two separate angels: Promoting PA in childhood and sustaining PA in adulthood.

Generally, PA in children and adolescents is positively correlated to physical fitness, cardiometabolic health, healthy bone development, mental health, cognitive function, academic performance, and weight management [35]. The focus in children is on two central effects: the prevention of obesity and associated health risks, and the prevention of a decrease in motor deficits and physical fitness [36]. This is crucial, as underlined by important study on the topic by Kimm et al. The authors found PA to decline without intervention to almost none over a 10-year study period in over 2000 girls from ages 9 to 19 with an increase of BMI and obesity at the same time [37].

Aside from such immediate examples about the importance of PA promotion and the avoidance of sedentary behavior, the habituality of PA is a third focal point in this concept. PA behavior has long been known to track from childhood over adolescence and into adulthood [38,39]. While in the very early years, tracking of PA is moderate over a one-year period [40], tracking in adolescence into adulthood was moderate to high over a 22-year observed timeframe [41]. The adolescent years appear to be very crucial in the formation of active adults. Additionally, in adults tracking of PA was moderate to high as well over 7-year periods in two respective studies [42,43]. Interestingly, Janz and colleagues found sedentary behaviors to track better than activity. Furthermore, maintaining high levels of vigorous activity and low levels of TV viewing is associated with favorable changes in adiposity [39]. In other words, active children will very likely develop into active adults. Developing good habits early on is easier than unlearning bad behavior later on, especially since tracking of obesity shows similar moderate to high correlations [41].

In adults, regular PA has a positive impact on the reduction of all-cause mortality, the development of cardiovascular disease, hypertension, specific cancers such as bladder, breast, colon or gastrointestinal, and type-2-diabetes. Furthermore, it improves mental health, cognitive function, quality of life, sleep, and prevents adiposity and falls [35]. Consequently, while PA in childhood deals mostly with setting up good habits for a healthy lifestyle, PA in adulthood is focused the prevention of secondary diseases.

Physical Activity and Health-related Quality of Life

The relationship between PA and mental health is worth exploring in some more detail at this point for further understanding of the projects of this dissertation. As previously mentioned, regular PA has a positive effect on mental health in the form of reduced symptoms of anxiety or depression in both children and adults [26]

In a world in which mortality is no longer viewed as the only endpoint of healthy or in the medical aftercare of chronically ill people, quality of life has more and more found its way

into the interest of researchers and medical professionals over the past three decades. Thereby, the emphasis is placed on the critical relationship between physical and psychological health and well-being. Health-related quality of life (HRQoL) is in this context defined as the understanding of self-perceived health and is a key component of a holistic approach to health and well-being of an individual [44,45].

Quality of Life and HRQoL are terms often used interchangeably. In more detail, the WHO defines it as an *»individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns«* [46]. This idea of quality of life takes into account physical, psychological, social, personal, and environmental states of well-being as well as relationships to others.

Other definitions of the concept quality of life exist, whether it be global definitions, definitions which cover certain domains of well-being, or approaches focused on the interest of a particular field of research. Even though it is a multidimensional and therefore rather complex construct, all definitions agree that quality of life generally entails an individuals' evaluation of his or her own life. Furthermore, quality of life is generally quite unique to an individuals' perspective on past experiences and future expectations [47-49].

Going into more detail about the connection between regular PA and HRQoL, general literature finds that higher levels of PA and lower levels of sedentary behavior are associated with higher HRQoL among children, adolescents and adults. The more physically active an otherwise healthy person the better their HRQoL [50,51] even though the exact magnitude of these effects has yet to be fully determined [52]. Interventions to increase PA have also been shown to increase HRQoL levels in children and adolescents [52].

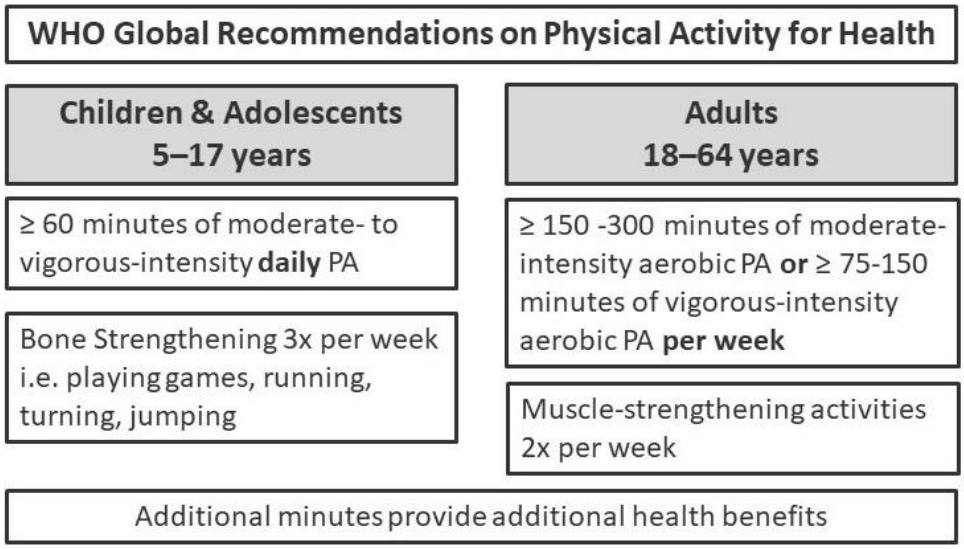
HRQoL has also been studied quite extensively in pediatric and adult patients with CHD. The findings, however, are quite mixed. While some studies find HRQoL in children with CHD to be worse than in healthy peers and increasingly worse with higher CHD severity [53], others find only physical subscales of HRQoL to be reduced [54], or HRQoL to be even better in children with CHD than in healthy [55]. In adult patients with CHD, the HRQoL seems to generally be worse than healthy, and worse in older patients and patients with more complex CHD [56-59]. The connection between PA and HRQoL in patients with CHD is explored only sparsely so far, even though there seems to be a positive connection between HRQoL and PA levels in this chronically ill population as well [60-63]. Therefore, one major purpose of this project was to explore the connection between PA and HRQoL in children with CHD which will be further elaborated in chapters to follow.

In clinical or public health settings, HRQoL is mostly assessed to quantify the effects of chronic illnesses, treatments, or disabilities. Thereby, questionnaires employing self-ratings on health status are used including but not limited to covering physical, mental, emotional, social, psychological, or life satisfaction domains. Quite a few different tools for measuring HRQoL in varying populations exist such as the *»Patient Reported Outcomes Measurement Information System Global Health Measure«* (PROMIS®) [64], *»Healthy Days«,* by the Centers for Disease Control and Prevention [65], or *»Behavioral Risk Factor Surveillance System«* (BRFSS) [66]. A popular tool for HRQoL assessment in children and adolescents is the KINDL® questionnaire which was also used for purposes of the project of this dissertation. It is a generic, internationally recognized questionnaire with 24 different items with different age-appropriate versions [67].

How much Physical Activity is recommended?

Very clear guidelines were published by the WHO in the form of *Global Recommendations on Physical Activity for Health* in 2010 [35], and updated in 2020 [26] (Figure 12) which outline detailed instructions for all age groups

Figure 12: WHO Recommendations on Physical Activity



This update is important to consider as minor changes in the phrasing have implications for the understanding of the publications of this dissertation. While the 2010 guidelines recommended adults to achieve 150 minutes of MVPA *in bouts of at least 10 minutes*, the 2020 update does not entail the recommendation for these 10-minute bouts anymore. Instead, now the official WHO guideline on PA and sedentary behavior recommends adults to achieve at least 150 minutes of MVPA throughout the week, regardless of bouts. Furthermore, regarding children, the initial 2010 guidelines asked for at least 60

minutes of MVPA *per day,* whereas the 2020 guidelines now ask children and adolescents to reach at least »an average of 60 minutes *per day across the week*«. This gives room for interpretation that the updated WHO guidelines are met if 60 minutes of MVPA are met every day on average, whereas previously the »hard« WHO criteria asked for 60 minutes of MVPA every single day. While these updates are minor and more concerned with phrasing, they need to be kept in mind when considering the publications of this dissertations. Publication I, II, and IV where composed and published when the initial WHO recommendation from 2010 was still in place. Furthermore, the measurement device for adults of the project of this dissertation (Garmin vivofit 3 – more details below) adhered to the initial WHO criteria from 2010 and therefore measured MVPA in bouts of 10 minutes.

For children, the WHO recommendation is focused on daily goals of 60 minutes across the week, while adults should just generate 150 minutes of PA per week independent of specific days. Additional PA minutes provide for additional health benefits. When these PA recommendations are not achievable, the WHO acknowledges that in either age group inactivity and sedentary behavior should be avoided at all cost and some activity is better than none [26]. As the focus of the publications within this dissertation were on young children, adolescents and adults, the recommendations for infants, toddlers, and senior citizens can be accessed elsewhere [26].

Other institutions such as the US Department of Health and Human services (USA), National Health Service (UK), the European Association for the Study of Obesity, or the Federal Ministry of Health (Germany) also publish similar but to slight degrees varying guidelines. However, as the WHO is the world's leading governing body on health, this is the generally agreed upon recommendation in the scientific field and will be the one adhered to in the following.

What about steps?

Contrary to popular belief, there are no specific international guidelines for daily steps. Counting steps as a mean of measuring distance is dating back into ancient times. Historically, Leonardo da Vinci is believed to be the inventor of the first mechanical step counter [68]. The origin of the nowadays well known 10,000 steps per day is, in fact, of commercial nature.

A company called *Yamax* designed a commercial step-counter and named it *manpo-kei* as a marketing-gig around the 1964 Olympic Games in Tokyo. The name roughly trans-

lates to '*10,000 steps meter'.* However, aside from purely commercial intends, this number did not relate to any scientific backing but rather indicated *»an active and healthy lifestyle«* in the company's opinion. Since then, research on step-count has gone a long way. Several studies have concluded that in most western countries the average person walks between 3,500 and 5,000 steps per day. If these people increased their daily count to 10,000, they would indeed be more physical active and thereby gain some health benefits [69]. Furthermore, previous researchers have attempted to translate current PA guidelines typically expressed in terms of duration, frequency, and intensity. Amongst young children, 13,000-15,000 steps per day appear to be associated with 60 minutes of daily moderate-to-vigorous physical activity (MVPA). For adolescents 10,000 to 11,700 daily steps may sum up to the recommended 60 minutes of MVPA [70]. Such a transfer of intensity related guidelines is a bit more difficult for adults as duration in a certain level of intensity plays a larger role in this population. Ultimately 7,000 to 10,000 steps per day is estimated to be beneficial and at least lead to some MVPA in adults [71]. Still, to date the WHO does not include a specific daily step goal in their *Global Recommendations on Physical Activity for Health* [26,35]

1.4 Physical Activity Measurement

Measuring PA has first found its way into scientific research in the early 1960s in the form of step counting [72]. Since then, PA measurement has followed an extensive development and several methods have emerged which can generally be divided into two categories: subjective methods and objective measures. Primary objective measures are the criterion standards *Direct Observation*, *Calorimetry*, and *Doubly Labeled Water Test,* while secondary objective methods usually describe all objective tools in the form of physiological measures and motion sensors. Lastly, subjective methods are sometimes also referred to as tertiary measures. Determination of the best method depends on the dimensions and domains of PA, the available material, financial and person resources, the setting which the method is employed, and how quickly the results are needed. In the following specific methods of both categories and their respective advantages and disadvantages will shortly be presented. This information was retrieved from two landmark publications on the topic: *The Guide to the Assessment of Physical Activity: Clinical and Research Applications. A Scientific Statement from the American Heart Association* [25] and *Physical Activity Assessment in Children and Adolescents* [73].

Objective Methods to assess Physical Activity

Criterion standards

All gold standard assessments are quite elaborate and require a larger number of resources, whether it be in a financial, spatial or in staff. Therefore, they are impractical for measuring PA per se, but are more extensively used to determine energy expenditure and to validate other subjective and objective measures in a laboratory setting.

Direct Observation is the criterion measure for PA patterns in which a trained observer follows subjects for a given period of time and notes activity or records videos to watch later. It is therefore quite time and labor intensive and more often used in younger subjects. While it is a good method to assess activity patterns, the presence of the observer might alter the activity behavior of the observed - a phenomenon that is commonly known as the *Hawthorne Effect*. It implies that subjects, when being observed or studied, might alter their behavior. It is a well-documented widely used term in research. While the conditions, under which the Hawthorne Effect occurs, as well as the mechanisms, effects, and magnitude of it are still relatively unclear, it is important to be kept in mind in any kind of health science research [74].

Calorimetry is based on the measurement of ventilatory volume and the respiratory intake of oxygen (O_2) and output of carbon dioxide (CO_2). Very broadly, the subject breaths

room air or a mixture of gases of known concentration while the expired amounts of both elements are analyzed. It can either be incorporated as testing at rest and / or during exercise and is a valid and accurate measurement for short-term energy expenditure. More details can be accessed elsewhere [75].

Doubly Labeled Water is the gold standard for measuring long-term energy expenditure. It is quite expensive and time-consuming and thus only used in very specific endeavors or case study settings. Foundation of the *Doubly Labeled Water* are the analysis of different elimination rates of two oxygen-18 (^{18}O) and deuterium (^{2}H). Both stable isotopes are consumed dissolved in water. After ingestion, ^{2}H is released from the body as water such as sweat, urine, or in the breath and ^{18}O as water and CO_2. Through regular saliva sampling over the observational process, the different elimination rates of both isotopes are gathered and then analyzed. The difference between the elimination rates of ^{18}O and ^{2}H are proportional to CO_2 production of the body and thereby an indicator of energy expenditure transferable into kcal or MET for further PA-related purposes. Depending on the size of the subject analyzed, the sampling period can last 5-14 days. More detailed information can be accessed elsewhere [76].

Physiological Measures and Motion Sensors

Aside from the criterion standards above, which are not useful for clinical settings or for larger research purposes, further objective measures of PA more suitable for everyday use exist. With the development of smaller and more accurate wrist-worn devices, popularity of these measures has increased substantially whether it be in a research or a commercial setting over the past decade [77]. Therefore, the following methods are more and more state of the art in PA assessment.
These objective methods generally all monitor and directly measure one or more biosignal as they occur and can be physiological measures such as heart rate monitors, motion sensors such as pedometers or accelerometers, and finally wearables which generally comprise of a combination of the other methods.

Physiological Measures such as heart rate monitoring as a form of assessing PA is based on the positive connection between heart rate and O_2-consumption (VO_2). In other words, an increase in heart rate is an indicator for cardiorespiratory stress and thus suggestive of movement such as PA or exercise. While it is not a very reliable measure at lower PA intensities, heart rate increases correspondingly with PA intensity it is quite valid of an assessment of time spent in certain intensity levels and therefore useful for

assessing and comparing PA patterns. Furthermore, it is inexpensive and requires minimal burden on the subject or the researcher. On the other side, however, is this method negatively impacted by the fact that factors other than physical movement can influence heart rate such as caffeine, environmental stress or emotional state of the subject tested.

Motion Sensors which capture movement of the body and translate it into estimate of PA can further be subdivided into *pedometers* and *accelerometers*.

Pedometers are relatively simple mechanical or electronic devices worn on ankle, waist or wrist used to quantify steps and estimate distance. Mechanical versions work with a spring mechanism, while more technical devices rely on location and motion tracking technology.

Accelerometers continuously detect and record accelerations and decelerations induced by bodily movement through microprocessors that in response to applied mechanical stress generate electric charge (so called piezoelectric transducers). Through microprocessors the recorded accelerations are converted into a digital signal quantified and referred to as *counts*. Thereby frequency, duration and intensity of acceleration and deceleration are measured. Generally, these counts are the units of acceleration due to gravity. The unit measure of counts is typically in meters per second squared (m/s^2). Motion can be detected in either single (vertical), two planes (vertical and mediolateral or vertical and anterior-posterior) or three planes (vertical, mediolateral, and anterior-posterior). The raw data of counts can then be transformed with the help of device specific prediction equations to estimate energy expenditure in kcal or MET and thereby translate into PA.
While such devices are objective and re-usable, they usually still require transformation and translation of raw data. This translation highly depends on device placement (ankle, waist, wrist). Furthermore, the ability to assess activities with limited torso movement such as cycling or strength training is limited.

Subjective Methods to assess Physical Activity

When employing subjective measures, two types of PA assessment are used. The assessed individual can either record activities as they occur in the form of a log or diary, or can recall previous activities based on PA questionnaires. These questionnaires entail either self-reported responses or interviews and can be subdivided into three categories varying in detail and length: *Global*, *recall*, and *quantitative history* (Table 5).

Table 5: Types of Physical Activity Questionnaires

Global	Recall	Quantitative History
- 2-4 items - Quick overview - Used to identify whether a person adheres to PA standard such as WHO criteria (yes / no) - Classification - Clinical setting or epidemiological studies	- 7-12 items - Self-administered - Focus on domains and dimensions of PA	- 20-60 items - Interview-based - Focus on time-period i.e. past month, year, decade etc. - i.e. types / intensities contributing to mortality

A diary or log on the other hand is usually a detailed record of an individual's PA and sedentary behavior on an hour-by-hour basis. The individual usually records the starting and end of the activity as well as its intensity throughout a day, a week, or a month. These records are later evaluated by a researcher. A global PA questionnaire was used throughout the projects of this dissertation to subjectively assess PA. A simple question about whether children or adults as subject of the included studies believe themselves to be physically active enough according to WHO criteria was thereby employed. More details will follow in the chapters below.

A recent analysis of 89 studies by Nascimento-Ferreira et al. on agreement estimates between subjectively and objectively assessed PA in healthy populations found the agreement between both methods to be weak to moderate. However, the authors state that these findings are not conclusive yet and further analysis on research on the topic is needed. While selection of a specific method largely depends on research purposes and resources available, objective measures might provide more valid insights [78].

Again, where it was not otherwise cited, the above information was retrieved from two landmark publications on the topic of measuring PA: *The Guide to the Assessment of Physical Activity: Clinical and Research Applications. A Scientific Statement from the American Heart Association* [25] and *Physical Activity Assessment in Children and Adolescents* [73].

Wearables

Recent technological advances have led to the development of relatively simple accelerometers, motion sensors and physiological measures into a combination of the above, and thereby into an exciting tool of PA assessment: *wearables*. Wearables are usually

monitors worn at the wrist and are generally of commercial nature. Wearables can also be clipped to clothing or are part of smartphone applications [77]. However, such devices embodied in clothing are beyond the scope of this dissertation. The focus from here on out will be on wrist-worn wearables, specifically on the *Garmin vivofit 3* model for adults (Figure 13) and *Garmin vivofit jr.* (Figure 14) devices for children and adolescents by Garmin Inc. (Olathe, KS, USA). These devices were also used throughout the projects this dissertation is based on.

Figure 13: The Garmin vivofit 3 wearable device for adults

Both models are wrist-worn PA trackers which track steps, distances, intensity minutes and calories burned, with only slight but substantial differences. The *Garmin vivofit jr.* is intended for children and adolescents up to 18 years old, whereas the *Garmin vivofit 3* is suitable for all adults over the age of 18. The devices differ in bandwidth, and the fact that in the *Garmin vivofit jr.* every active minute counts from the very beginning, while the in the *Garmin vivofit 3* only continuous bouts of 10 minutes are credited for. This means that in the adult model active minutes are only recoded if an activity is continuously sustained for at least 10 minutes. Stopping for more than 60 seconds will require the subject to move uninterruptedly for another 10 consecutive minutes before s/he will start earning intensity minutes credit again. Thus, the adult model Garmin vivofit 3 is in line with the initial WHO recommendations on PA [35].

The validity and accuracy of the Garmin vivofit devices have been established in a variety of settings, and in comparison to the previously mentioned gold standards of assessing energy expenditure and PA. The device showed excellent correlations with energy expenditure assessed through indirect calorimetry at various walking and running speeds, and constant and varying velocities [79], as well as in monitoring step count and different intensities levels of PA [80]. Aside from this comparison to energy expenditure criterion measures, the device has more intensively been validated against direct observation. Thereby, the Garmin vivofit devices showed high accuracy and excellent validity across

different age groups at various speeds and intensities [81-83] and across a variety of daily living activities [84]. The device even showed excellent reliability against the direct observation in patients after stroke [85] and patients with chronic heart failure [86]. The wearable device seems to reach its limits in accuracy only in subjects using rollators [87] and crutches [88].

Figure 14: Garmin vivofit jr. device for children and adolescents

The devices are waterproof which allowed a more complete monitoring of the subjects included in the studies for this dissertation. They transform the gathered information into active minutes and different levels of PA intensity by an inbuilt algorithm. This occurs through the translation of step frequency of at least 100 steps per minute into active minutes. Every activity below this step frequency merely adds to the step count while activities above this threshold also count toward active minutes. Activities with higher frequencies result in proportionally more active minutes recorded. The devices add minutes spent in moderate intensity and vigorous intensity for a final amount of active minutes, or MVPA. Taking a brisk walk or going out for a jog that lasts for at least 10 consecutive minutes will trigger credit towards the active minute count of the subject wearing the device in the *Garmin vivofit 3*. The cadence for a brisk walk needs to be about 100 steps a minute to record moderate active minutes and more than 130 steps per minute to earn vigorous active minutes in the adult model [89]. The thereby used »Move-IQ« technology detects the type, mode, frequency, and duration of activities. Unfortunately, the exact data transformation process is proprietary [90]. Furthermore, required step cadence for the *Garmin vivofit jr*. is not publicly accessible either.

Commercially available fitness trackers and wearables are a large consumer market. In late 2016 more than 400 different devices were available globally with every 1 out of 10 adults in the United States wearing some sort of PA monitor [77].This consumer market is

predicted to grow to 1 out of 8 people owning some sort of fitness tracking devices worldwide [91,92].

Consumer wearables offer such a wealth of information and possibilities, that the user and researcher can get lost quite easily [77]. Therefore, for this project it was important to have a relatively simple device to ensure high patient compliance and adherence. As the projects of this dissertation were to a large degree focused on the very basic cross-sectional analysis of a patient cohort, it was important to focus on the basics. The *Garmin vivofit* devices are in fact quite simple and affordable, yet with a long battery life and feasible for clinical research [93]. Furthermore, the *Garmin vivofit jr*. was at the start of this project the first and only fitness tracking device available specifically designed for children and adolescents. Therefore, these models were optimally suited for the project. However, it is important to mention that these devices are commercially available consumer models with the main goal of promoting a physically active lifestyle. The company claims that the sensors are quite precise yet they cannot be compared with accuracy of medical devices, but merely provide good estimates [94].

2 Purpose of the Project

»Only what gets measured, gets managed«

Peter Ferdinand Drucker – Austrian economic researcher and consultant

Considering the above established concepts and themes around CHD, PA, and its measurement, the question of why it would be interesting or even important to attend to PA measurement in patients with CHD arises.

In the past, physicians, cardiologists, and medical personnel have been hesitant in their medical aftercare of patients with CHD due to fear of heart failure or sudden cardiac death, especially in terms of PA restrictions [95]. The perspective has been narrowed to functional outcome and survival. Since survival is nowadays ensured through major advancements in prenatal diagnostics and surgical correction techniques, the horizon has now broadened to a more holistic approach in medical aftercare also considering other impairments beyond cardiac issues [96]. Together with a previously hesitant attitude in cardiologists when it comes to exercise prescription, CHD is still a sensitive subject for parents-to-be who might become overprotective of their chronically ill children [97,98]. In reality however, with just very few exceptions, almost all patients with CHD are encouraged to reach regular PA recommendations [35] of the general population as it is safe and beneficial [10,99]. Additionally, patients with CHD still have decreased physical capacity and are – even though there have been major improvements in the past -susceptible for increased mortality [100,101]. Regarding the prevention of secondary diseases increasing physical capacity and physical fitness is of great importance in this patient population. Especially considering that in these patients there is a training effect – and thereby a positive impact on physical capacity – even at low intensities [102]. Put more simply, physical active patients will most likely have a longer and better life.

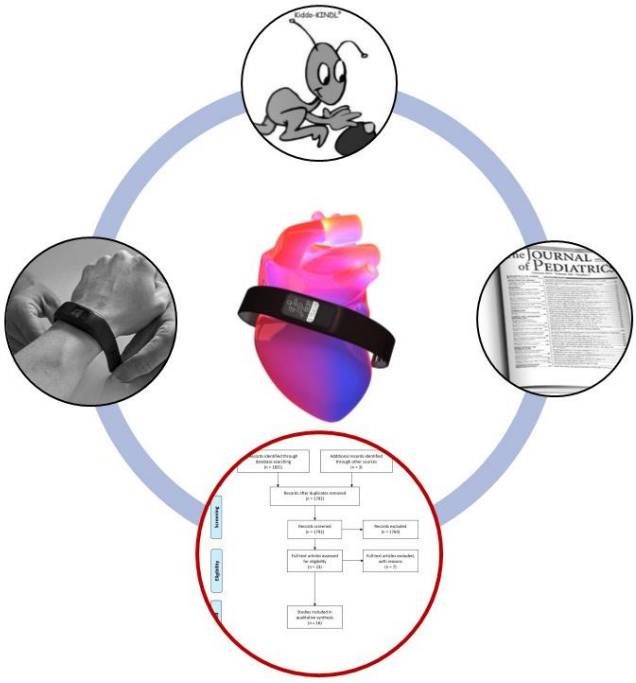
Specialized centers which are in charge of routine follow-ups of patients with CHD have changed over to implement encouragement towards an active lifestyle into their medical aftercare about two decades ago. Yet it is unclear to what extent these encouragements have landed on fertile ground and succeeded in achieving a more physically active CHD population. Ultimately, the goal is to further improve and enhance patient care and patients' lives. Only if it is known how active patients with CHD really are, can in the next step areas for possible improvements and interventions from this knowledge be derived.

In order to attain the aforementioned knowledge, four scientific studies were published in fulfillment of this dissertation underlining the main purposes of this project:

1. Give an overview on the current state of literature on objective PA research in patients with CHD.
2. Determine with objective measures how active children and adults with CHD really are on a daily basis and whether there is an association between objectively assessed PA and HRQoL in these children.
3. Determine the level of agreement between self-reported and objectively measured PA in patients with CHD.

3 Publications

In a first publication, the current state of the literature of the past ten years has been assessed. Therefore, a systematic literature review was carried out to give an overview about quality, methodology and outcomes of scientific work of the past decade on accelerometers objectively assessing PA in patients with CHD patients. As laid out below, the focus was on objectively rated quality of the study, the characteristics of the different accelerometers used, and a first attempt to answer the question whether patients with CHD are active enough. On a short side note, objective PA and exercise capacity as well as quality of life was also explored. The goal was to provide a holistic assessment of the current literature on the topic. This is important as objectively assessed PA via wearable devices is a relatively new field of research.



3.1 Objective Physical Activity Assessment in Clinical Congenital Heart Disease Research: A Systematic Review on Study Quality, Methodology and Outcomes

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Conflicts of Interest:

No conflict of interest. No competing interests for any of the authors.

Individual contribution:

The PhD candidate Leon Brudy is the principal author of this paper. He developed and carried out the systematic search strategy. Along with his Co-Author Michael Meyer, he screened and assessed the search results, Luisa Garcia-Cuenllas was the third reviewer in case of disagreement. Leon Brudy finally drafted the manuscript. Jan Müller revised the manuscript. Alfred Hager, Renate Oberhoffer, and Peter Ewert all gave input to further improve the manuscript. Leon Brudy under supervision of Jan Müller handled the submission process until final publication.

Abstract

Background: The shift towards a preventative approach in medical aftercare of congenital heart disease (CHD) patients has led to encouragement of regular physical activity (PA) in this patient population. Objective measures are crucial in accurately displaying PA levels and have increasingly found their way into clinical research. This review aims to give an overview about quality, methodology and outcomes of current scientific work on accelerometers objectively assessing PA in patients with CHD.

Methods: Systematically researched literature in all relevant databases (PubMed, Cochrane, Scopus) over the past decade (2009-2019) with history of CHD and accelerometer-based PA assessment was evaluated by two independent reviewers according to the Study Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Heart, Lung, and Blood Institute.

Results: Eight articles with 664 pediatric patients with CHD aged 3 - 18 years (range 10-162 patients), five studies with 574 adults with CHD aged 18-63 years (range 28-330 patients), and three studies with 177 pediatric patients and adults with CHD aged 8 to 52 years were included. Two studies were rated »Good«, 9 »Fair«, 5 »Poor«. Methodologies and devices differed substantially across all studies.

Conclusions: Overall study quality was fair at best and due to difficult methodological comparability of the studies no clear answer on how active patients with CHD really are can currently be given. Larger studies carefully considering collection and processing criteria, and correct reporting standards exploring PA in patients with CHD from different angles are needed.

Introduction

Regular physical activity (PA) has long been known as one of the most effective preventative tools for a vast number of diseases and clinical conditions, especially those of cardiovascular origin [2,103]. Patients with congenital heart disease (CHD) have inhibition to different extends within their cardiovascular system since birth, and with increased survival medical aftercare has shifted towards prevention of secondary diseases in this patient population [10]. Part of this preventative approach is the encouragement to regular PA and sports participation [11] as it is now considered beneficial without additional risk for almost all patients with CHD. The encouragement towards a generally physically active lifestyle becomes imperative in this context [10]. Technological advances offer exciting research opportunities [104] and since subjectively estimated PA fails to draw accurate pictures [105], objective measures to assess PA have also found their way into clinical CHD research. After more than a decade of research assessing PA with accelerometers in

CHD patients it is time to evaluate where the field is at and where it needs to go from there. Therefore, this review aimed to give an overview about quality, methodology and outcomes of current scientific work on accelerometers objectively assessing PA in CHD patients.

Material and Methods

Search strategy

A systematic literature research referring to January 2009 until December 2019 was conducted in the electronic databases PubMed, Cochrane and Scopus. Two independent reviewers identified relevant original articles and randomized controlled trials (RCT) in English language. A standard protocol with search terms was generated according to the population, intervention, comparison, outcome, context (PICO-C) [106] method and connected as followed:

1. Congenital heart disease OR congenital heart diseases OR congenital heart defect OR congenital heart defects AND
2. physical activity assessment OR physical activity measurement OR physical activity OR daily activity OR accelerometer OR accelerometry OR wearable OR activity tracker OR activity monitor OR fitness tracker

Medical Subject Headings terms and similar filters (clinical trial, randomized controlled trial, published in the last 10 years, humans, English language) were used and appropriately adapted if necessary. According to the latest Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [107], supplementary reference lists were analyzed to detect further eligible articles.

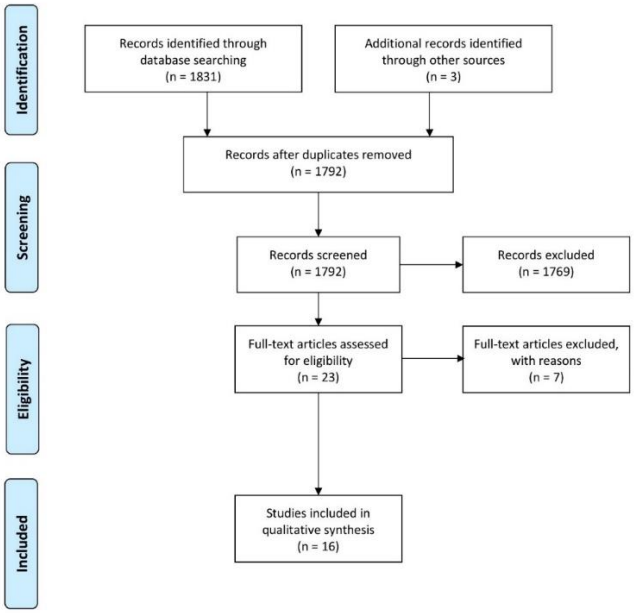
Data collection

Both reviewers screened all relevant articles for titles and abstracts which had to fulfill the basic inclusion criteria: History of CHD and accelerometer-based PA assessment. PA had to be classified in some sort of PA intensity and not merely step count alone as moderate-to-vigorous physical activity (MVPA) is shown to be beneficial for cardiovascular health [108].

At least one of the two reviewers had to consider a reference eligible. A third reviewer was consulted to resolve disagreement before and during full text analysis.

Both reviewers rated the included literature according to the Study Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Heart, Lung, and Blood Institute [109] - a 14-item list assessing potential risk for bias - and consequently categorized them as good, fair, or poor.

Figure 15: Search and selection process for systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)



Results

Description of selected studies

Figure 15 displays the search and selection process. Reasons for exclusion after full-text analysis were: 1 study protocol [110], 2 validation studies [111,112], 4 studies without reporting PA intensity [113-116]. Overall, 16 articles with a total of 1415 CHD patients met all inclusion criteria.

8 studies [61,117-123] evaluated 664 pediatric patients with CHD aged 3 - 18 years (range 10-162 patients), 5 studies [124-128] 574 ACHD aged 18-63 years (range 28-330 patients). Three studies [129-131] with 177 patients (range 30-99 patients) examined both pediatric patients and adults with CHD aged 8 to 52 years but did not report results separately for these age ranges. Detailed information on study types and quality rating can be found in Table 6.

Table 6: Quality assessment according to the NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

Study	Type	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality Rating
PEDIATRIC CHD (n=8)																
Kao et al. 2009 [117]	CSS	✓	✓	✓	-	-	✓	-	-	✓	NA	✓	-	✓	-	Poor
Ewalt et al. 2012 [118]	CSS	✓	✓	✓	✓	✓	-	-	NA	✓	-	✓	-	✓	-	Fair
Longmuir et al. 2013 [119]	RCT	✓	✓	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	Good
Stone et al. 2015 [120]	CSS	✓	✓	✓	-	-	-	-	NA	-	-	✓	-	✓	-	Poor
Klausen et al. 2016 [121]	RCT	✓	✓	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	Good
Banks et al. 2017 [61]	CSS	✓	✓	-	-	-	✓	✓	✓	✓	-	✓	-	✓	-	Poor
Voss et al. 2017 [122]	CSS	✓	-	CD	✓	-	✓	-	NA	✓	-	✓	-	✓	✓	Poor
Brudy et al. 2019 [123]	CSS	✓	✓	-	✓	-	✓	✓	✓	✓	-	✓	-	CD	✓	Fair
ACHD (n=5)																
Dua et al. 2010 [124]	CCT	✓	✓	-	✓	-	✓	✓	✓	✓	✓	✓	-	✓	-	Fair
Müller et al. 2012 [125]	CSS	✓	✓	-	✓	-	-	-	NA	✓	-	✓	-	✓	✓	Fair
Sandberg et al. 2016 [126]	CSS	✓	✓	✓	✓	-	✓	-	NA	✓	-	✓	-	✓	✓	Fair
Opotowsky et al. 2018 [127]	RCT	✓	✓	✓	✓	-	✓	✓	-	✓	✓	✓	-	✓	✓	Fair
Larsson et al. 2019 [128]	CSS	✓	✓	✓	✓	✓	✓	-	✓	✓	-	✓	-	✓	-	Fair
PEDIATRIC AND ACHD (n=3)																
Müller et al. 2009 [129]	CSS	✓	✓	✓	✓	✓	-	-	-	✓	-	✓	-	✓	-	Fair
Duppen et al. 2015 [130]	RCT	✓	✓	-	-	✓	✓	✓	-	✓	✓	✓	-	✓	-	Fair
Hedlund et al. 2016 [131]	CCS	✓	-	✓	-	-	-	-	NA	✓	-	✓	-	✓	-	Poor

CD: cannot determine, NA: not applicable, ✓ denotes “Yes”, - denotes “No”; RCT: randomized controlled trial, CCT: controlled clinical trial, CSS: cross-sectional study, CHD: Congenital Heart Disease, ACHD: Adults with Congenital Heart Disease, NHLBI: National Heart, Lung, and Blood Institute

The majority of cross-sectional studies (CSS) compared their CHD population to a healthy reference cohort (RC) [117,118,120,123,126,128,131], the remaining [61,122,125,129] compared PA within their CHD sample. All but 4 studies [61,119,121,127] compared their patients' PA to a healthy RC, against varying institutional PA recommendations, or against both. All CSS evaluated total daily (and where applicable weekly) PA, MVPA or separate PA intensities including sedentary time. Subjective PA was also compared in 7 CSS [117,120,123,128,131]. 3 CSS [61,125,129] and 1 RCT [130] examined QoL, and 3 CSS exercise capacity parameters [61,125,129] in relation to PA.

Intervention studies lasted 12-months in pediatric patients with CHD [119,121], 12-weeks in adolescents and young adults with CHD [130], and 10 or 12 weeks in ACHD [124,127]. Alongside increasing PA these studies also focused on other parameters beyond of the scope of this review (exercise capacity, QoL, gross motor skill). Table 7 provides further information on cohort description, outcome measures, and PA classifications.

Accelerometers used

Detailed information on technicalities and characteristics of the devices used in all included studies can be found in Table 8. The majority of studies aimed to collect data on PA for all 7 days of the week [61,118-120,122-125,127,131]; 1 study each collected data for 6 [121] and 5 [130] days, 2 sampled for 4 days [126,128] and 2 older studies [117,129] assessed PA over 3 days. All studies recorded activity during waking hours. Sandberg et al. [126], Larsson et al. [128] and Hedlund et al. [131] additionally utilized a 24-hour protocol.

Sampling epoch length of the accelerometer devices differed between the studies [61,118,119,122-126,128,129,131 121 120] and ranged from 3 to 60 sec. Three studies [117,127,130] did not report about their devices' sampling epochs at all. Only Voss and colleagues [122] and Hedlund and colleagues [131] reported the sampling frequency (30 Hz) of their devices. Detailed listings of frequency and epoch are displayed in Table 8.

Daily PA in different levels of activity (sedentary, light, moderate, vigorous) or MVPA were assessed in all studies. However, thresholds, wear-time algorithm and PA intensity classification for different activity levels differed or were not reported at all. Four studies [123,126-128] did not report how accelerometer data was transferred into PA intensity, in 2 studies [121,124] PA could not be determined.

Table 7: Study Characteristics and Outcomes

Study	CHD n (female)	Healthy CG (n)	CHD Diagnosis (n)	Age ± SD (range)	Outcome Measures Intensity Classification	Guideline	Results
PEDIATRIC CHD (n=8)							
Kao et al. 2009 [117]	34 (17)	age & gender matched (34)	VSD (16), ASD (7), ToF (11)	10.5 (9-12)	Objective and subjective TEE, Average total daily EE, EE in MVPA PAL [132], subjective MVPA Schofield (1985) [133]	PAL > 1.63 Mega-joule/day (0.025 x age + 1.40) Hoos et al. 2003 [134]	No difference in MVPA between pediatric CHD (188.6 ± 181.9) and RC (223.4 ± 201.6, p=.60), also not on weekends (180.1 ± 235.8 vs 154.0 ± 158.5, p=.71). TEE and PA lower for boys with than without CHD. TEE did not differ between girls with and without CHD. Girls with higher PA than boys.
Ewalt et al. 2012 [118]	21 (16)	sex & grade-in-school matched (21)	CoA (5), Hypoplastic left heart (4), VSD (3), ASD (1), D-TGA (1), PS (1), Bicuspid aortic valve & stenosis (1), mitral valve prolapse (2), DILF (1). ToF (1), Tricuspid Atresia (1)	10.7 ± 3.2 (6.6-17.1)	time in total PA: total counts / 30 sec./day. SED: ≤ 50 counts per 30 sec. period. Moderate PA: 4.0 – 6.9 MET, vigorous PA: ≥ 7 MET. Average daily PA. Freedson et al. (2005) [135]	≥60 min of moderate PA and/or vigorous PA/day. American Alliance for Health, Physical Education, Recreation and Dance [136]	No difference in PA min (287.2 ± 110.1 vs. 262.0 ± 57.5, p=.23), MPA (57.5 ± 37.9 vs. 50.7 ± 23.9, p=.26), or VPA (13.1 ± 12.4 vs. 9.9 ± 5.9, p=.28) in CHD vs. CG. 20% of CHD reached ≥60 min of moderate PA and/or vigorous PA/day. Majority of time (52%, 6.7 of 13 monitored hours) spent in SED. >1/5 of all reach ≥60 MVPA min /day
Longmuir et al. 2013 [119]	61 (25)	-	All after Fontan procedure	9.1 [IQR: 7.7; 10.5]	Daily MPVA as sum of all counts exceeding 400 per 15-sec epoch min/week Gross Motor Development; Health-related fitness, hand grip strength, hamstring flexibility, CPET, activity attitudes Puyau et al. (2004) [137]	-	MVPA increased to 36 ± 31 min/week (p=.04) above baseline and was sig. greater (p=.03) than predicted age decrease at 2-year FU in IG; no association between weekly MVPA min and diagnosis (p=.29), left-or-right ventricle physiology (p=.55), years since Fontan operation (p=.76), or use of ACE-inhibitors(p=.31); no difference in MVPA in rural vs. urban patients (p>.05).
Stone et al. 2015 [120]	10 (4)	age-, sex-, data- acquisition-season-matched (10)	CoA (6), ToF (4)	4.0 ± 1.0 (3-5)	SED: <8 counts / 3 sec, light PA: 8-83 counts / 3 sec, moderate PA: ≥84 and <168 counts / 3 sec, MVPA: ≥ 84 counts / 3 sec, vigorous PA: ≥ 168 counts / 3 sec Parent-estimated PA habits of child Pate et al. (2006) [138]	≥180 min of any PA type PA/day Canadian Physical Activity Guidelines for the Early Years [139]	No difference in total (219 ± 39.9 vs. 224.1 ± 44.0, p=.80), light (147.5 ± 22.3 vs. 143.8 ± 21.7, p=.71), moderate (44.0 ± 11.8 vs. 48.1 ± 12.7, p=.46), MVPA (71.9 ± 22.6 vs. 80.3 ± 24.5, p=.43), or vigorous (27.9 ± 11.7 vs. 32.2 ± 13.1, p=.45) PA minutes/day between pediatric CHD and CG. Only 40% of CHD and CG reached ≤180 min PA/day. 90% of parents reported their children as active as healthy, and 80% of parents 1-3 hours daily screen time.

Klausen et al. 2016 [121]	158 (66)	-	CoA (52), TGA (35), Fallot (21), DORV (7), Truncus arteriosus (4), AVSD (9), TCPC (6), other (24)	14.6 ± 1.3 (13-16)	Total MVPA min/day: >2000 accelerometer cut-point counts / min CPET -	-	No difference in MVPA min/day between IG (40.3 ± 21.8) and CG (41.3 ± 22.9). 32% of IG and 26% of CG reached ≥60 MVPA min/day at baseline. Adding tailored eHealth did not affect outcomes in adolescents with CHD.
Banks et al. 2017 [61]	137 (59)	-	ASD (31), TGA after Switch (34), ToF (37), Fontan (35)	8.5 ± 2.1 (4-12)	Total daily and weekly MVPA >1600 counts/min CPET, Gross Motor Skill, QoL Puyau et al. (2004) [137]	-	No difference in MVPA between CHD groups (p=.68). Higher MVPA was associated with higher overall self-efficacy (p=.02) and trend towards higher %-predicted VO_2 (p=.052) but not RER, CHD type or gross motor skill percentile (p >.05 for all).
Voss et al. 2017 [122]	81 (34)	-	Mild (26): 6 Bicuspid aortic valve; 5 VSD, 4 AS, 4 ASD, 3 mixed aortic valve disease, 2 PS, 1 mitral valve disease, 1 PDA Moderate (26): 11 ToF, 7 CoA, 2 AS, 1 total anomalous pulmonary venous return, 1 ostium primum ASD, 1 sinus venous ASD, 1 EBS, 1 Shone syndrome, 1 Pentalogy of Cantrell Severe (29): 17 Fontan, 8 TGA, 2 DORV, 2 valved conduit Cardiac Transplants (9)	13.6 ± 2.7 (8-19)	Total PA: sum of vertical acceleration counts, MVPA: ≥2296 CPM,vigorous PA: ≥4012 CPM, % of SED time relative to valid accelerometer wear time, subjective PA Evenson et al. (2008) [140]	60 min. of MVPA on ≥6 days/week. Canadian Health Measures Survey [141]	No difference in various PA intensities between CHD severity groups. Boys were sig. more active than girls (49.2 [33.1-67.2] vs. 39.2 [25.1-46.9], p=.006). Age (-3.2 [-5.3, -1.1] p<.01) and sex (-14.7 [-25.9, -3.5], p<.05) related declines in MVPA min/day. Median daily MVPA was 43 (IQR: 28.9-56.9) min/day. 8% (12% boys, 4% girls) reached ≤60 MVPA min on ≤6 days/week.
Brudy et al. 2019 [123]	162 (60)	yes (96)	29 simple, 58 moderate 74 complex, 1 not defined Left heart obstruction (28), Right heart obstruction (53), Isolated shunts (20), TGA after Switch (19]) TCPC (25), Miscellaneous (17)	11.8 ± 3.2 (5.8-17.6)	Daily Steps and MVPA, subjective PA -	≥ 60 MVPA min/day WHO [35]	No difference in daily MVPA min (80.5 ± 25.6 vs. 81.5 ± 25.3, p=.767), only lower step count (10206 ± 3178 vs. 11142 ± 3136, p=.040) between pediatric CHD and CG. 76% CHD and 84% CG reached ≥60 MVPA min/day (p=.217) while age (p=.004), higher BMI (p=.002), overweight & obesity (p=.016) and complex CHD severity (p=.046) were associated with not reaching it. Subjective estimation fairly correct in about half the patients.
ACHD (n=5)							
Dua et al. 2010 [124]	61 (17)	-	NYHA class I (21) NYHA class II (16)	31.7 ± 10.9 (18-63)	Objective PA as accelerometer counts / hour. MVPA: >	5 x 30 min MVPA/week	MVPA min/day increased from 21.9 ± 17.1 to 39.1 ± 27.0 (p<.001), 14% reached 5 x 30

			NYHA class III & IV (13)		2100 CPM, activity associated EE, subjective PA QoL, treadmill exercise test -	UK National Guidelines for PA [142]	MVPA min/week at baseline and 56% at FU (Group I: 23.9% to 80.9%, Group II: 12.6% to 37.6%, Group III: 0% to 38.5%). All groups sig. increased subjective & objective PA, QoL, treadmill test duration, and AAEE.
Müller et al. 2012 [125]	330 (149)	-	Native or palliated Cyanotic (16), Fontan (42), TGA after atrial switch (59), TGA no atrial switch (13), EBS (7), ToF (56), PS (18), CoA (23), AS (37), Isolated Shunts (35), Other (14)	30.0 ± 8.4 (18-61)	Daily PA: 7 day mean activity units. Daily moderate: 3-6 MET, >984 CPM, vigorous: >6 MET, >2340 CPM, and MVPA: sum of activity >3 MET QoL, CPET Rowlands et al. (2004) [143]	≥30 MVPA min/day Center for Disease Control & Prevention [144]	59.2 ± 39.7 of ≥ moderate PA min/day, 76% reached ≥30 MVPA min/day. Moderate relationship between daily activity and exercise capacity (r=0.437, p<.001), poor between QoL and PA (r=0.030 to 0.258, p>.05 for all). Reduced exercise capacity in most patients (73.7 ± 19.5% of predicted).
Sandberg et al. 2016 [126]	80 (32)	age & sex matched (42)	Simple (40): 12 CoA, 3 AS, 3 Aortic Regurgitation, 4 AS, 14 VSD, 1 ASD, 1 PFO, 1 PDA, 1 Mitral Regurgitation complex (40): 5 TGA, 2 ccTGA, 8 ToF, 3 PA, 2 DORV, 1 DILV, 7 TCPC, 2 Fontan, 3 EBS, 6 Eisenmenger, 1 Miscellaneous	Simple: 30.0 (20.7) Complex: 33.7 (29.4) Median (IQR)	Total accelerometer counts/day, MVPA min/day No classification	≥150 MVPA min/week - averaged to 21.4 MVPA min/day WHO [35]	No difference in MVPA or in reaching PA recommendations between ACHD and CG or according to NYHA class. 54% of simple, 45% of complex CHD, and 56% of CG reached ≥ 21.4 MVPA min/day (p>.05 for all). Simple CHD (107.7 [76.6, 139.1]) had more accelerometer counts/day than complex (72.8 [49.2, 101.0], p≤.001), CG (78.3 [58.7, 106.9], p=.002). Impaired NYHA class predicted PA better than CHD complexity.
Opotowsky et al. 2018 [127]	28 (14)	-	ToF (3), TGA (9), Fontan (2), pulmonary atresia (2), truncus arteriosus (1), EBS (1)	41.1 ± 12.1 (29-53)	Daily vector magnitude and counts, SED, light PA, MVPA, MVPA % CPET, QoL, self-reported health status, blood markers No classification	-	No difference in MVPA min/day, step count or estimated MET between groups at baseline and various FU (p>.05 for all). Cardiac Rehabilitation is safe and associated with improvements in aerobic capacity and subjective health status
Larsson et al. 2019 [128]	75 (29)	age & sex matched (42)	Simple (39), complex (36)	37.5 ± 15.5 (22-43)	Time spent at MVPA (≥3 MET), subjective PA No classification	≥150 MVPA min/week - averaged to 21.4 MVPA min/day WHO [35]	No difference in proportion reaching ≥ 21.4 MVPA min/day (48.0 vs. 57.1%, p=.34) between ACHD and CG, or between simple and complex CHD (53.8 vs. 41.7%, p=.29). ACHD and CG overestimate weekly PA level.
PEDIATRIC AND ACHD (n=3)							
Müller et al. 2009 [129]	57 (18) 28 ≤14 &	-	DILV (21), Tricsupid Atresia (15), hypoplastic left heart syndrome (11), hypoplastic	14 [IQR: 11.0; 17.8]	Daily activity: mean value of activity units over 3 days. Time in moderate: 3-6 MET, >970	≥60 min, ≥3 MET, ≥5 days/week	Patients spent 87 (48-112) MPA and 12 (6-24.5) VPA min/day. 72% of CHD patients reached ≥60 min, ≥3 MET, ≥5 days/week.

	29 ≥14 years		right heart syndrome (5), DORV with imbalanced ventricles (3), AVSD with imbalanced ventricles (2)	(8-52)	CPM and vigorous PA: >6 MET, >2333 CPM CPET, QoL Rowlands et al. (2004) [143]	UK Expert Consensus Group [145]	MVPA was associated with age (r=-0.506, p<.001) and VO_{2peak} (r=0.432, p=.001) Daily PA was related to QoL in children <14 years (r=0.380, p=.046).
Duppen et al. 2015 [130]	99 (66)	-	ToF (47), Fontan (43)	15 ± 3 (10-25)	Counts / min. converted to MET, time in sedentary, moderate, vigorous, and very vigorous activity CPET Freedson et al. (2005) [135]	≥ 60 MVPA min/day WHO [35]	MVPA was 104 ± 65 min/day (13.6 ± 8.6% of measured time) and did not change in IG or CG. 70% reached ≥60 MVPA min/day at baseline and FU. Male patients (69.9 +-44.8) were more active than female (46.3 +- 27.6; p<0.001). Peak VO_2 and workload increased in IG but not CG. Sig. increase in TOF but not Fontan patients in VO_{2peak}.
Hedlund et al. 2016 [131]	30 (14)	age & sex matched (25)	Fontan (30)	14.2 ± 3.2 (8.9-20.4)	Total vector magnitude. Sedentary: 0-100 CPM, light: 101-2292 CPM, moderate: 2293-4008 CPM, or vigorous: ≥4009 CPM, subjective physical exercise QoL Evenson et al. (2008) [140]	≥ 60 MVPA min/day WHO [35]	No difference in MVPA min/day (148 ± 60 vs. 141 ± 54, p=.67), less time in SED (48.6 ± 4.4 vs. 51.8 ± 5.2%, p<.05), more light PA (41.1 ± 3.3 vs. 38.4 ± 3.6%, p<.01), similar MPA (10.3 ± 4.2 vs. 9.8 ± 3.7%, p=.67) between CHD patients and CG. Age-related decrease in MVPA in patients (R^2=0.18, p<.05). 90% of patients reached ≤60 MVPA min/day. Patients subjectively reported less time exercising and lower QoL than CG.

CHD: Congenital Heart Disease, ACHD: Adults with Congenital Heart Disease, NYHA: New York Heart Association, CoA: Coarctation of the Aorta, TGA: Transposition of the Great Arteries, DORV: Double-outlet right ventricle, DILV: Double-Inlet left ventricle, ASD: Atrial Septal Defect, TCPC: Total Cavopulmonary Connection, ToF: Tetralogy of Fallot, EBS: Ebstein Anomaly, AS: Aortic Stenosis, PS: Pulmonary Stenosis PDA: Patent Ductus Arterious, PFO: Persistent Foramen Ovale, cc-TGA: congenital-corrected TGA, CTP: Cardiac Transplant Patients, CG: Control Group, IG: intervention group, SD: Standard Deviation, SED: Sedentary Behavior, QoL: Quality of life, PA: Physical Activity, MVPA: moderate-to-vigorous PA, MPA: moderate PA, VPA: vigorous PA, TEE: total energy expenditure, CPET: Cardiopulmonary exercise test

Table 8: Physical Activity Assessment Characteristics

Study	Device	Placement (waterproof)	Assessment length	Data Inclusion Criteria	Sampling Frequency	Sampling epoch (sec)
PEDIATRIC CHD (n=8)						
Kao et al. 2009 [117]	RT3	Hip (No)	3 days starting on Friday waking hours	-	-	-
Ewalt et al. 2012 [118]	ActiGraph 7164	Hip (No)	7 consecutive days waking hours	≥10h of data for 3 week-days and 1 weekend day	-	30
Longmuir et al. 2013 [119]	Respironics Actical 2.1	Hip (Yes)	5 school days and 2 non-school days waking hours	≥8h of data on 3 school days and 1 non-school day	-	15
Stone et al. 2015 [120]	ActiGraph GT1M	Hip (No)	7 consecutive days waking hours	≥5h on ≥4 days incl. 1 weekend day	-	3
Klausen et al. 2016 [121]	ActiGraph 77	Hip (No)	6am - 10pm for 4 weekdays and 2 weekend days at baseline and FU	≥10h of data on ≥1 weekend day and 1 weekday	-	5
Banks et al. 2017 [61]	Respironics Actical 2.1	Hip (Yes)	5 school days and 2 non-school days waking hours	≥10h of data on ≥3 school days and 1 non-school day	-	15
Voss et al. 2017 [122]	ActiGraph GT3X+ and GT9X	Hip (No)	7 consecutive days waking hours	≥600 min/day of data on ≥3 days	30 Hz	15
Brudy et al. 2019 [123]	Garmin vivofit jr.	Wrist (Yes)	7 consecutive days waking hours	3 weekdays and 1 weekend day	-	60
ACHD (n=5)						
Dua et al. 2010 [124]	ActiGraph 7164	Hip	7 consecutive days	-	-	60

		(No)	waking hours			
Müller et al. 2012 [125]	RT3	Hip (No)	7 consecutive days waking hours	-	-	60
Sandberg et al. 2016 [126]	ActiHeart	Chest (No)	4 consecutive days 24 hours	-	-	30
Opotowsky et al. 2018 [127]	ActiGraph GT3X+	Hip (No)	7 consecutive days at baseline and FU waking hours	≥600 min/day of data on ≥3 days	-	-
Larsson et al. 2019 [128]	ActiHeart	Chest (No)	4 consecutive days 24 hours	-	-	30
PEDIATRIC AND ACHD (n=3)						
Müller et al. 2009 [129]	RT3	Hip (No)	3 consecutive days waking hours	-	-	60
Duppen et al. 2015 [130]	ActiGraph GT3X	Hip (No)	5 consecutive days waking hours	≥8 hours/day on ≥3 days	-	-
Hedlund et al. 2016 [131]	ActiGraph GT3X	Wrist (No)	7 consecutive days 24 hours	-	30 Hz	60

Discussion

Study Quality

The majority of studies was rated »Fair« at best with more than a third showing substantial risk for bias with a »Poor« rating. Qualitative flaws were mostly found in missing power or effect size, low participation rate or very small cohorts. The lack of key confounding variables in the analysis, no blinding of accessors and an unclear subject selection (Table 6) leaves room for stronger studies in the future. Major statistical and methodological flaws - like reporting inconsistent p-values in the abstract vs. results section [61] or calculating PA thresholds using an adult recommendation [132] for a cohort of preschool children [117]- should be avoided .

Accelerometer Characteristics

Unless sleep data is relevant a protocol sampling during waking hours with minimum of 4 valid data days including 1 weekend day is recommended [146]. A 7-day protocol is even more advisable, especially in younger participants [147] Three studies [126,128,131] utilized a 24-hour recording protocol, the rest sampled just during waking hours. Only 3 separate studies [118,119,123] actually adhered to these valid day inclusion criteria (Table 8).

All but two studies [123,131] used hip-worn devices . Overall, a possible tradeoff between classification accuracy and compliance in hip vs. wrist-worn devices needs to be considered. Ideally studies should be designed with both hip and wrist worn devices.

Only 2 studies reported sampling frequency [122,131] and none data filters of their devices. Even though exact information tends to be proprietary, it has a major impact on data interpretation and comparability and therefore should be included as detailed as possible in future studies. Highest possible sample-frequency is recommended in multiples of 30 [146]. The younger the subjects, the shorter the epoch length to capture sporadic movements [146]. In light of the WHO recommendation asking for bouts of ≥10 minutes [35] sporadic movements become more negligible and longer sampling epochs are suitable in adults [146]. All studies in ACHD and young adults reported to adhere to this employing 30-60 sec. sampling epochs. In pediatric studies epoch length differs (Table 8) and future studies should focus on using the shortest sampling epoch possible. It is recommended to follow the same epoch length and intensity classification criteria which were used in the original calibration study of the respective device. As internal algorithms differ by manufacturer data processing is device specific. Therefore, it is advisable to use the

default intensity classifications. Table 9 contains further recommendations for the application of objective PA assessment in clinical research.

Table 9: Recommendations for the application of PA assessment in clinical research

Sampling protocol	7-day sampling period ≥ 4 valid days incl. 1 weekend day capturing all waking hours Clear data inclusion criteria defined
Device placement	Possible tradeoff between hip (better for intensity classification accuracy) & wrist-worn (better for wear-time compliance) devices to consider Ideally both in research settings
Sampling frequency	Highest possible in multiples of 30
Epoch length	Shorter (3-10 sec) in children & adolescents to capture sporadic movement Longer (30-60 sec) in adults
Intensity classification	Follow initial calibration study guidelines or default settings of the device
PA guidelines / reference	Age & region / country appropriate guidelines must be employed Preferably WHO criteria and country specific guidelines Own recruited healthy reference cohort is advisable
Confounders to consider	Age, sex, BMI, CHD severity, weather, seasonality
Cohort size	Current studies have been limited to a maximum of a few hundred patients included. Larger cohorts are needed

Are Patients with CHD active enough?

With a few very specific exceptions, almost all patients with CHD can and should be encouraged by their physician and medical care-takers to achieve general population guidelines for PA [10,148]. Those are according to the World Health Organization: Children and adolescents aged 5–17 should accumulate at least 60 minutes of MVPA daily with greater benefits above 60 minutes. Adults aged 18–64 should reach at least 150 minutes of moderate-intensity aerobic PA throughout the week or do at least 75 minutes of MVPA throughout the week or an equivalent combination of both intensities [35]. Further specific recommendations on indications, type and intensity for PA and exercise in patients with CHD can be found in international guidelines [11,149,150].

Pediatric Patients with CHD

None of the 4 CSS comparing pediatric patients with CHD to a reference cohort (RC) found a difference between patients and healthy in daily PA or MVPA [117,118,120,123].
Only 1 [123] found their patients reaching the WHO recommendation for children and adolescents. The remaining 3 [118,121,122] followed quite inactive cohorts in regards to their respective age-related PA recommendations. The cohort of Stone et al. [120] was also quite inactive but was compared to the Canadian Physical Activity Guidelines for the Early

Years [139] with some of their patients being older than the used institutional recommendation.

2 CSS without RC evaluated PA in regard to CHD severity or CHD subgroups and did not find differences in mean MVPA [61,122], while others [123] reported complex CHD to be associated with not meeting the WHO recommendation on PA.

While 2 studies [122,123] report a decrease in daily PA with increasing age, Longmuir et al. [119] were able to keep MVPA constant through an intervention study over 22 month long-term FU contrasting the expected decrease in daily PA with age. Furthermore, all 3 studies dealing with pediatric and ACHD (but generally rather young cohorts) found an age-related decrease in PA [129-131].

Even though the influence of weather and seasonality on PA behavior has been demonstrated [151], only a few studies controlled their results [119,122,123] therefor. One [119] found an association between spring season and PA in pediatric patients with CHD.

Pediatric and ACHD

Müller and co-workers [129] found 72% of patients with total cavo-pulmonary connection to reach ≥60 min activity ≥3 MET on ≥5 days per week [145]. Similarly, Duppen et al. had 70% of patients meeting ≥60 MVPA min/day at baseline before heading into intervention. Young male patients were significantly more active than female [130] which was also confirmed in ACHD [126]. However, Duppen et al. [130] did not improve daily PA or percentage of MVPA time through 12 weeks aerobic training in an already active young cohort. In contrast, Hedlund et al. [131] showed 90% of their young population to reach ≤60 MVPA min/day, an overall similar measured MVPA for patients and age-and-sex-matched RC, and an age-related MVPA decrease. Furthermore, patients spent less time sedentary and more time in light activity than RC [131].

ACHD

One of the 3 CSS [125] reported 76% of ACHD to be fairly active reaching ≥30 MVPA min/day, while the other two [126,128] found no differences in MVPA against a healthy RC and in the proportion that reached the WHO guideline [35]. The latter two also found about half of all ACHD and RC not reaching daily PA recommendations. It is important to note, that both Sandberg et al. and Larsson et al. [126,128] calculate the WHO recommendation as 21.4 MVPA min/day. However, the WHO recommends to split the ≥30 MVPA min/day in bouts of ≥10 minutes [35]. Therefore, these results need to be interpreted carefully.

The clinical controlled-trial (CCT) [124] and the RCT [127] conducted in ACHD did not use a healthy RC. Dua and colleagues [124] increased the adherence to the UK National Guidelines for PA [142] from 14% to 56% and mean MVPA minutes almost doubled after 10 weeks intervention. Furthermore, patients with higher NYHA class were less active at baseline and more able to improve their PA through training. Contrary, Opotowsky and colleagues [127] found only a trend towards more MVPA time, and no difference regarding PA at baseline and FU after 12 week cardiac rehabilitation intervention vs. standard of care.

Generally, it seems like the older the cohorts, the less active CHD patients are both against healthy RC and institutional PA recommendations. Few of the herein mentioned interventional studies tried to improve PA showing mixed results on the efficacy of these interventions. Large studies with a focus on CHD subgroups do currently not exist.

PA and Exercise Capacity

Eight studies determined parameters for physical capacity, mostly through cardio-pulmonary exercise testing (CPET) in CHD patients, but four reported CPET outcomes separately [119,121,127,130], while one [124] only examined maximal walking time without associating PA. Müller and colleagues found a moderate relationship between daily activity and exercise capacity [125] and PA to be reduced in patients with lower VO_{2peak} [129], while Banks et al. (2017) [61] found only a trend in the association between MVPA and higher percent-predicted VO_2. All three studies did not have a healthy RC.
Considering the importance of exercise capacity in predicting mortality in CHD patients [102] future studies should explore the association to PA in this population more in detail. In a similar physiological context, there is no information on the relationship between daily PA and cardiovascular risk in CHD patients. Exploring this triumvirate of objectively measured PA, exercise capacity, and cardiovascular risk holds potential for further studies and eventually improving medical aftercare in CHD patients.

PA and Quality of Life

Müller et al. [125] found only a poor correlation between daily PA and several QoL domains in ACHD. In pediatric patients with CHD, Banks and co-workers [61] showed higher MVPA to be associated with higher self-efficacy in pediatric patients with CHD, while Müller and colleagues [129] found QoL to be related to daily activity in children with CHD younger 14 years. Duppen et al. [130] confirmed weak correlation between self-estimated QoL and daily PA in adolescents and young ACHD. Hedlund and co-workers [131] sampled but did not analyze PA in relation to QoL. Therefore, clear answer on the relationship between

objective PA and QoL in CHD patients can currently not be given leaving room for future, large scale studies.

Limitations

Sample size of the majority of included studies was generally small. Comparison between studies presented difficulties because device types and characteristics, data classification criteria and the guidelines PA was measured against differed substantially.
The majority of studies were cross-sectional, five were interventional. The main goal of this review was to compare the status quo by evaluating quality of methods, outcome measures and results and not to assess interventions of the separate studies. Therefore, we decided to critically appraise all articles according to the NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. We acknowledge that to evaluate the intervention quality the NHLBI Quality Assessment of Controlled Intervention Studies is the appropriate tool for RCT or CCT. However, both questionnaires contain similar key methodological items.

Conclusion and Clinical Recommendation

The methodology and assessment of PA was fair at best in most of the studies. Due to methodological differences of the studies, no clear answer on how active CHD patients really are can currently be given.
Objective PA measures are crucial in identifying patients at risk for inactivity. Therefore, larger studies adhering to consistent measuring and reporting standards exploring PA in CHD patients, also in the context of different angles such as exercise capacity or QoL, are needed. These studies should employ their own healthy RC and compare PA against institutional guidelines. Future studies need to consider device placement, sampling protocol and frequency, epoch length, intensity classification thresholds, valid day inclusion criteria and wear-time definition more carefully.

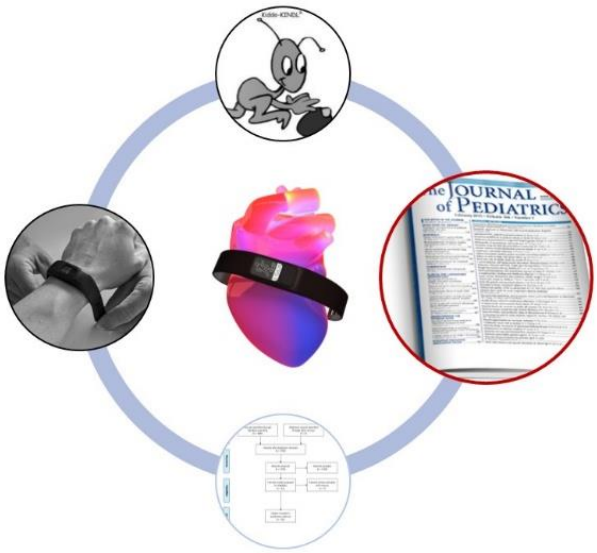
3.2 Discussion of Publication I

Aside from the previously mentioned methodological differences and the difficulties in comparing the studies' results, this systematic review also revealed some further insights about objectively assessed PA in patients with CHD. Commercially available PA tracking devices are still underutilized in clinical research. Only 16 studies published on the topic gives potential to further research perspectives. Especially when it comes to assessing PA in young participants, these devices can in fact be of great value. Therefore, in the following original article, the focus was on bringing this new technology and the clinical pediatric population at the German Heart Center Munich together. In a first analysis, parts of the gathered data of the project were cross-sectionally evaluated to determine how active the children with CHD are in comparison to otherwise healthy children. As an additional insight, the focus was also on whether there are discrepancies between how active children believe themselves to be and how active they really are.

At this point it is important to reiterate that this publication was composed and published before the WHO Guidelines on Physical Activity were updated in 2020 [26]. Therefore, at certain points the publication is still referring to required PA in bouts of at least 10 minutes for adults, which are in line with the 2010 WHO recommendation [35]. The 2020 update [26] does not include the requirement of bouts of 10 minutes anymore.

Due to a relatively lengthy publication process of the previous article »Objective Physical Activity Assessment in Clinical Congenital Heart Disease Research: A Systematic Review on Study Quality, Methodology, and Outcomes«, the following article »Children with Congenital Heart Disease are active - but need to keep moving. A cross-sectional study using wrist-worn physical activity trackers« was also included in the systematic review as it was published beforehand. Thereby, the unique opportunity of assessing our own study in the context of others provided itself. This brought valuable insights and further improvements for the project at the German Heart Center Munich. The lengthy publication process underlines the fact, that objective PA assessment in patients with CHD is a niche topic. Yet the international publication attributes to the importance of this approach in a holistic medical aftercare of these patients.

The three publications of cross-sectional studies to follow now bridge the gap towards objective PA research in a clinical setting and provides imperative findings in the context of how active patients with CHD really are.



3.3 Children with Congenital Heart Disease are active – but need to keep moving. A cross-sectional Study using wrist-worn Physical Activity Trackers.

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Conflicts of interest:

No conflict of interest. No competing interests for any of the authors.

Individual contribution:

The PhD candidate Leon Brudy is the principal author of this paper. Together with the Co-authors Michael Meyer and Anna-Luisa Häcker he sampled the data in the study center, and along with Julia Hock he statistically analyzed the data. Leon Brudy also drafted the manuscript and presented the results. Jan Müller was responsible for conception and supervision of the study design, and revised the manuscript. Alfred Hager, Renate Oberhoffer und Peter Ewert all gave important input to improve the manuscript. All authors have read and approved the final version of the manuscript. Under supervision of Jan Müller, Leon Brudy handled the submission process until final publication.

Abstract

Objective: To compare daily physical activity (PA) of children with congenital heart disease (CHD) to healthy peers measured with wearables bracelets in a large cohort. Additionally, subjectively estimated and objectively measured PA was compared.

Study Design: From September 2017 to May 2019, 162 children (11.8 ± 3.2 years, 60 girls) with various CHD participated in a self-estimated and wearable-based PA assessment. Step-count and moderate-to-vigorous physical activity (MVPA) were recorded with the Garmin vivofit® jr. for seven consecutive days and compared to a reference cohort of 96 healthy children (RC, 10.9 ± 3.8 years, 49 girls).

Results: Children with CHD were remarkably active and 123 (75.9%) achieved 60 minutes PA on a weekly average according to the WHO criteria as 81 (84.3%) of the healthy peers did (p=.217). After correction for age, sex and seasonal effects, only slightly lower step-count (CHD: 10206 ± 3178 steps vs. RC: 11142 ± 3136 steps, p=.040) but no lower MVPA (CHD: 80.5 ± 25.6 min/day vs. RC: 81.5 ± 25.3 min/day, p=.767) occurred comparing CHD to RC. In children with CHD higher age (p=.004), overweight or obesity (p=.016), complex severity (p=.046) and total cavopulmonary connection (p=.027) were associated with not meeting WHO criteria. Subjective estimation of daily MVPA was fairly correct in half of all children with CHD.

Conclusions: Even though the majority is sufficiently active, PA needs to be promoted in overweight or obese patients, patients with complex CHD severity, and in particular in those with total cavopulmonary connection.

Introduction

Physical activity (PA) as a cornerstone of physical and mental health has long been known to ensure regular development in both healthy and chronically ill children [11]. Almost all patients with congenital heart disease (CHD) should therefore achieve general population guidelines for PA since it is considered beneficial and without additional risk [10,148]. As PA behavior is habitual and tracks well into adulthood its promotion in childhood is imperative for optimal cardiovascular health later on [38,152]. Long term cardiovascular health and physical well-being are especially important in the context of an ageing cohort of patients with CHD. The lack of PA not only takes potential benefits away – inactivity is also associated with tremendous health burden, particular those of cardiovascular origin [153].

Assessing PA in children is challenging and different methodologies entail benefits and flaws alike. Whereas recalling PA in questionnaires lacks objectivity, more valid and reliable pedometers and accelerometers are often bulky, require technical expertise, are expensive and not necessarily appealing to young children [73,154]. Furthermore, findings on childhood activity in CHD are conflicting. Smaller studies on children with complex CHD reported lower PA [155-157] whereas more recent studies on a broad spectrum of CHD revealed these children to be of similar activity as healthy peers [117,118,120,122,158]. Commercially available activity trackers, known as wearables, offer an opportunity for unique insights and have already been used in other clinical pediatric settings [159-161] and in small cohorts of children with CHD [116,162]. While an overall clear picture of PA in children with CHD is lacking, the reliability, validity and objectivity of such wearables has been validated [79,93,163].

Therefore, the aim of this study was to find out how active children with various CHD are compared to healthy peers as measured in daily steps and moderate-to-vigorous physical activity (MVPA), which refers to an energy cost of ≥3 metabolic equivalents, using wearables. Furthermore, subjectively estimated and objectively measured PA in children with CHD was compared.

Participants and Methods

Study Participants

From September 2017 to May 2019, 162 children with various CHD (11.8 ± 3.2 years, range: 5.8 - 17.6; 60 girls) participated in a wearable-based PA assessment for seven consecutive days. Detailed information on the study subgroups is given in Table 10.

All patients were recruited during their routine follow-up at the outpatient department of the German Heart Center Munich to participate in an ongoing cardiovascular screening study. They were free of any neurological diseases or acute infections and in good general health without sport restrictions. CHD severity according to ACC criteria [19] was distributed as follows: 74 complex, 58 moderate, 29 simple. For one patient with arrhythmia severity class could not be defined. For comparisons 96 healthy controls (10.9 ± 3.8 years, range: 5.8-17.6 years, 49 girls), who had to meet the same inclusion criteria as the clinical population (free of neurological diseases or acute infections, good general health, no sports restrictions) were recruited from several schools, after-school care facilities and kindergartens, with parts of this data already published elsewhere [93]. Children and parents gave written informed consent after being provided with information about

the study protocol. The study was conducted in accordance with the declaration of Helsinki (revised 2008) and approved by the local ethical board of the Technical University of Munich (project number: 314/14).

Table 10: Study Subjects

	n	Sex (female) n (%)	Age Mean ± SD	BMI z-score Mean ± SD	Steps Mean ± SD	MVPA Mean ± SD
LHO	28	9 (32.1%)	10.4 ± 3.4	-0.80 ± 1.04	10889 ± 3447	88.7 ± 28.6
RHO	53	19 (35.8%)	12.0 ± 2.6	-0.34 ± 1.30	9424 ± 2915	73.5 ± 23.2
Isolated Shunts	20	12 (60.0%)	13.0 ± 3.5	-0.02 ± 0.91	9428 ± 3172	78.2 ± 27.9
TGA after Switch	19	3 (15.8%)	12.1 ± 3.2	-0.30 ± 1.05	11546 ± 4107	89.4 ± 25.6
TCPC	25	8 (32.0%)	12.4 ± 3.4	-0.55 ± 1.93	8701 ± 2540	69.9 ± 22.9
Miscellaneous	17	9 (52.9%)	10.5 ± 3.8	-0.53 ± 1.36	9587 ± 2852	82.4 ± 25.1
CHD	162	60 (37.0%)	11.8 ± 3.2	-0.42 ± 1.32	11772 ± 9832	84.1 ± 24.2
RC	96	49 (51.0%)	10.9 ± 3.8	-0.15 ± 0.92	9832 ± 3225	79.0 ± 26.5
p-value*	-	**.037**	**.035**	.083	**<.001**	.125

*significant with p<.05, T-test comparing CHD to RC, CHD: children congenital heart disease, RC: reference cohort

Objective Physical Activity Assessment

For objective PA assessment all children were in presence of their guardians instructed to wear a Garmin vivofit® jr. (Garmin Ltd. Olathe, KS, USA) wrist bracelet for seven consecutive days starting one day after they received the device. The Garmin vivofit® jr. is a wearable specifically designed for children, which tracks PA in steps and every single MVPA minute throughout the day. All children were instructed to wear the bracelet during all their waking hours including when showering, swimming, leisure time and organized sports, with possible removal overnight. They were further instructed to transfer accumulated steps and MVPA at the end of each day on a provided report card. 238 (92.2%) of the children had complete and valid reports for objective PA on seven consecutive days. 20 (7.8%) patients had incomplete data but at least three weekdays and one weekend day (four days in total) were present which allowed to calculate a weekly average.
For statistical purposes, steps and MVPA minutes for every day were analyzed and also computed to a weekly average according to current World Health Organization (WHO)

criteria [35]. Currently the WHO recommends the following levels of physical activity for children aged 5-17 years:

1. At least 60 minutes of moderate- to vigorous- intensity physical activity daily.
2. Amounts of physical activity greater than 60 minutes provide additional health benefits.
3. Most of the daily physical activity should be aerobic. Vigorous-intensity activities should be incorporated, including those that strengthen muscle and bone, at least 3 times per week.

Subjective Physical Activity Assessment

In addition to the objective MVPA measurement, children with CHD subjectively estimated their days of activity before receiving the wearable (»On how many days of an average week are you active for at least 60 minutes per day?«). This question was answered by the child on a Likert scale from none to seven.
The answer of the subjective PA assessment was used to analyze the number of days children with CHD subjectively estimate themselves to be active for 60 minutes or more. For healthy children, subjectively estimated data was not recorded.

Data analyses

All data are shown in mean ± standard deviation (SD). Data were analyzed via T-test and Chi-Squared test. To compare the primary outcome variables daily steps and MVPA between children with CHD and healthy peers an adjusted univariate ANOVA with covariates sex, age, and season (spring, summer, fall, winter according to calendar season) was used.

Self-reported PA was compared to objectively measured PA data with intraclass correlation coefficient (ICC). Logistic regression was used to determine possible parameters age, sex, BMI, CHD severity, CHD type and whether CHD underwent surgery or not, are associated with meeting the WHO guidelines of 60 minutes of PA on a weekly average. We defined meeting the WHO guidelines as mean daily MVPA ≥60 min/d like Voss and colleagues [122]. Thereby we are applying the »soft« WHO criteria for MVPA as a weekly average. The much harder variant to interpret the criteria is ≥60 minutes of PA on every single day. However, since it has been shown that every minute of MVPA is beneficial [108] this article focuses more on MVPA minutes and not on threshold levels. All data were analyzed using SPSS 25.0 software (IBM Inc., Armonk, NY, USA) with a two-tailed level

of significance at p-value ≤ .05. Figures were drawn using R Studio (RStudio Team. RStudio: Integrated development for R. Boston: RStudio, Inc. 2015.).

Results

Physical Activity Assessment

Children with CHD were remarkably active. According to the WHO criteria 123 (75.9%) children with CHD and 81 (84.3%) of the healthy peers (p=.217) accumulated 60 minutes PA on a weekly average. After correction for age, sex and seasonal effects, only a slightly lower step-count (CHD: 10206 ± 3178 steps vs. RC: 11142 ± 3136 steps, p=.040) but no lower MVPA (CHD: 80.5 ± 25.6 min/day vs. RC: 81.5 ± 25.3 min/day, p=.767) occurred. Evaluating the distribution on weekends and weekdays, both groups were more active during weekdays and less active on the weekend (p<.050 for MVPA and step-count). Only during the weekend children with CHD performed fewer steps (mean difference 1687 ± 526; p=.004) than their healthy peers (Table 11).

Table 11: Univariate ANOVA for steps and MVPA in children with CHD vs. healthy controls, split into weekdays and weekend adjusted for sex, age and seasonal effects

Steps				
	CHD (n=162) Mean ± SD	**RC (n=96) Mean ± SD**	**Mean Difference ± SEE**	**p-value***
Whole week (mean)	10206 ± 3207	11142 ± 3341	-936 ± 454	**.040**
Monday-Friday (mean)	10717 ± 3525	11372 ± 3664	-655 ± 499	.191
Weekend (mean)	8917 ± 4072	10604 ± 4242	-1687 ± 577	**.004**
MVPA				
	CHD (n=162) Mean ± SD	**RC(n=96) Mean ± SD**	**Mean Difference ± SEE**	**p-value**
Whole week (mean)	80.5 ± 26.2	81.5 ± 27.3	- 1.1 ± 3.7	.767
Monday-Friday (mean)	83.6 ± 27.7	83.5 ± 28,9	- 0.1 ± 3.9	.987
Weekend (mean)	72.8 ± 33.8	76.8 ± 35.2	- 3.9 ± 4.8	.405

*significant with p<.05; CHD: congenital heart disease, RC: reference cohort, MVPA: moderate-to-vigorous physical activity, SEE: standard error of the estimate.

Parameters associated with meeting the WHO Guidelines

As seen in Table 12, in the logistic regression, higher age (p=.004) and higher BMI (p=.002) were associated with not meeting the WHO criteria of 60 minutes of PA on a weekly average. Per definition of a BMI above the 90th percentile (30), 12 (7%) of children with CHD and 7 (7%) healthy peers were overweight or obese. Furthermore, 7 (58%) overweight / obese children with CHD and 1 (14%) overweight healthy peer failed to

reach the WHO criteria of 60 minutes of PA on a weekly average. Univariate logistic regression (Table 12) showed that in overweight or obese children with CHD the likelihood of meeting the WHO criteria of 60 minutes of PA on a weekly average was just 21.2% of children with CHD with normal weight (p=.016). In children with complex CHD the likelihood of meeting the WHO criteria was 46.7% (p=.046) of healthy peers (Table 12). In patients with total cavopulmonary connection the likelihood was even only 32.9% (p=.027).

Table 12: Univariate logistic regression for independent parameters associated with meeting the recommendation of 60 minutes of MVPA on a weekly average in children with CHD.

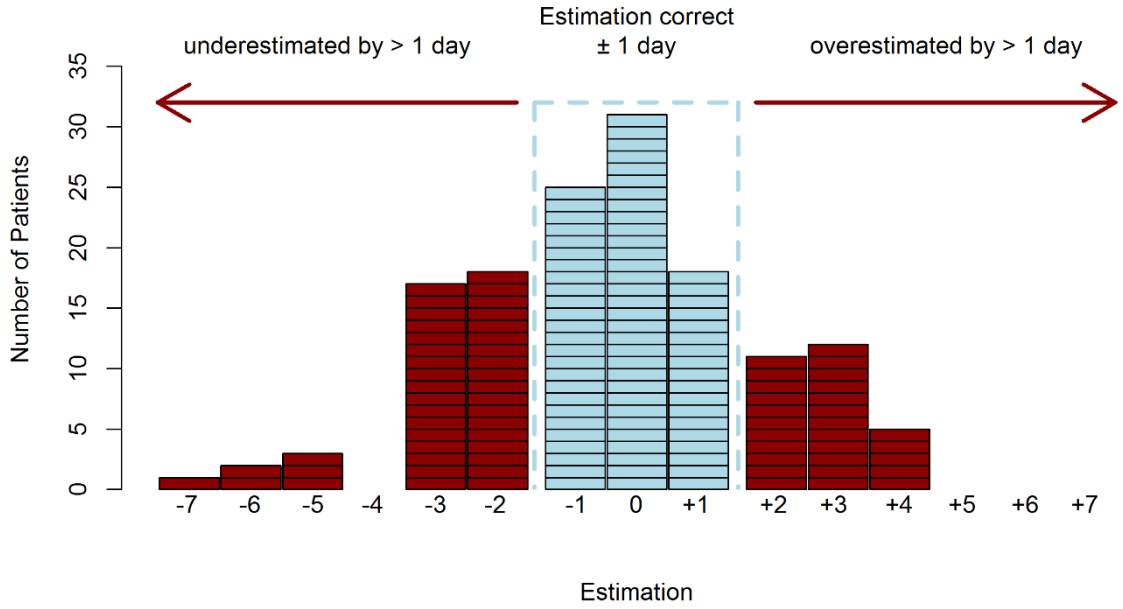
	Odds ratio (95% CI)	**p-value***
Sex (female)	0.696 (0.334 – 1.448)	.332
Age (years)	**0.841 (0.746 – 0.948)**	**.004**
BMI (kg/m²)	**0.866 (0.790 – 0.949)**	**.002**
Body Composition		
Normal weight (Reference)	1	
Overweight or Obese	**0.212 (0.060 – 0.748)**	**.016**
Status		
Healthy (Reference)	1	
Native CHD	0.654 (0.267 – 1.601)	.353
Surgery for CHD	0.610 (0.305 – 1.219)	.162
Severity		
Healthy (Reference)	1	
Simple	0.889 (0.293 – 2.697)	.835
Moderate	0.641 (0.280 – 1.466)	.292
Complex	**0.467 (0.221 – 0.987)**	**.046**
Season		
Summer (Reference)	1	
Spring	1.533 (0.623 – 3.771)	.352
Fall	0.653 (0.255 – 1.672)	.374
Winter	1.350 (0.491 – 3.714)	.561
Diagnostic Subgroup		
Healthy (Reference)	1	
Left Heart Obstruction	0.852 (0.280 – 2.593)	.778
Right Heart Obstruction	0.469 (0.208 – 1.058)	.068
Isolated Shunts	0.741 (0.217 – 2.525)	.631
TGA after arterial Switch	0.988 (0.256 – 3.812)	.986
TCPC	**0.329 (0.123 – 0.882)**	**.027**
Miscellaneous	0.864 (0.221 – 3.378)	.834

*significant with p<.05; CHD: congenital heart disease, TGA: Tetralogy of Fallot, TCPC: Total cavopulmonary connection

Subjective vs. objective PA

Children with CHD subjectively estimated to be active on 4.7 ± 1.8 days per week. Objective PA measurements via the wearable revealed them to reach 60 or more minutes of MVPA on 5.0 ± 1.9 days of the week. Overall, 75 (52.1%) children with CHD estimated their days of reaching 60 or more minutes of PA correct or were off by just one day, while 28 (19.4%) overestimated and 41 (28.5%) underestimated their daily PA by more than one day. Intraclass correlation (ICC) revealed a moderate association of self-reported and objectively measured PA in children with CHD (r=.495, p<.001). Detailed overview on the agreement is given in Figure 16.

Figure 16: Agreement of subjective vs. objective assessment of physical activity in children with congenital heart disease



Discussion

The findings in this study showed the majority of children with CHD to be sufficiently active considering their MVPA on a weekly average against the current WHO guidelines on activity and in comparison to healthy peers [35,108,164]. Nevertheless, PA needs to be promoted in overweight or obese patients, patients with complex CHD severity and in particular in those with total cavopulmonary connection because it is more likely that these subgroups do not meet the WHO requirements.

So far, two studies have used wearables to assess habitual PA in small cohorts of children with CHD. Voss and colleagues [162] made a validation study of a wearable against

an accelerometer in 30 children with CHD, while Jacobsen and colleagues [116] used wearables to monitor adherence in a home activity program in 14 children with Fontan circulation. Our study is the first using a wearable along with subjective estimation to assess habitual PA in a large sample size of children with various CHD. Furthermore, while many commercially available wearables are intended for adults, the herein used device is specifically designed for children, therefore allowing conclusions about daily activity in a young cohort.

Particularly MVPA has special significance for the cardiovascular system and is imperative for exercise capacity in patients with CHD [165]. Considering this cohort in general, a large number of children accumulated an average of 60 minutes of MVPA throughout the week without there being any difference between children with CHD and healthy controls. Only after looking on steps and MVPA, corrected for cofounders, children with CHD performed about 10% fewer steps, mainly due to the weekend. Nevertheless, this can be regarded as secondary because there was no difference in MVPA minutes between children with and without CHD. These results are impressive because many, mostly older studies and studies with non-objective measurement methods often come to a different result concluding limited MVPA in children with CHD [155-157]. In contrast, our results now suggest that the recommendations on PA in children with CHD are being widely implemented [10] and the physicians advice regarding the potential benefits of exercise for patients with CHD is now better accepted – even at specialists clinics [95]. This is imperative because an active lifestyle or sports participation is not associated with increased risk of adverse events in children with CHD and specific restrictions only apply in case of specific medical issues [99,166]. In fact, participation in competitive sports and increased frequency of MVPA are independently associated with a higher quality of life, improved physical capacity and lower BMI in adolescents and young adults with CHD [167]. This is especially vital in the light of known reduced exercise capacity and its association with hospitalization and death in patients with CHD [102,168,169]. Based on the results of our study, together with these previous findings, the earlier mentioned habituality of PA and the importance of childhood PA for optimal cardio-metabolic development [38,152], children with CHD still need to be encouraged to be active.

Parameters associated with meeting the MVPA Guidelines

While a general PA assessment is time consuming and expensive [73] it is useful to focus on risk groups. High BMI or overweight and obesity is considered the most crucial parameter because it is relevant for all children with CHD and inversely associated with

MVPA. Therefore, as a clinical implication, it might be considerable to assess MVPA at least in obese, and preferable also in overweight children. Afterwards children and their parents should, if necessary, be counseled on how they can increase MVPA or implement dietary steps to reduce weight and avoid long-term cardiovascular burden.

Also, patients with complex CHD severity, especially those with total cavopulmonary connection, should be in the focus as well, because the probability that these children with complex CHD meet the WHO guidelines is declined by half compared to the healthy peers. Lower age-dependent PA in patients with total cavopulmonary connection has already been reported previously [129]. In several articles it has been speculated about possible reasons. Overprotection due to parents and reluctant medical doctors who refrain to prescribe PA is one issue [97]. Also, the obvious functional limitation of complex lesions make it more difficult to maintain more intense PA for a longer time [12]. Nevertheless, encouragement, controlled sport classes and rehabilitation are possibilities to enhance MVPA in these patients [95].

Finally, just as in healthy children higher age was associated with fewer MVPA. However, since the recommendation for adults is just 30 minutes MVPA on five days of the week this point is negligible [35]. It is only important to ensure that active exercise behavior is initiated at an early age, because activity patterns track habitually and active children usually remain active during youth and adulthood [38,152].

Objective vs. subjective MVPA assessment

In general children tend to overestimate their MVPA [73]. Despite this our results show that half of our cohort generally seems to have a good feeling of how active they are as 52% of all children with CHD estimated themselves correctly or were just off by not more than one day. Nevertheless, the other half of participants over- or underestimated their MVPA. Underestimation might not be as critical as overestimation, since those children at least perform more MVPA than they assume. However, in both cases it still could be too little overall, and both groups could benefit from specific encouragement of reaching sufficient levels of daily MVPA. From our perspective it seems therefore reasonable to combine subjective and objective measurements in clinical practice to harmonize perception and reality.

Furthermore, accurately assessing PA remains a challenging yet vital research endeavor in children with CHD [154]. The findings of this study underline the importance of objective and reliable measures in clinical pediatric settings as subjective reports in the form of

questionnaires lack accuracy. Routine exercise testing is insightful in determining functional status but lacks the ability to determine habitual PA which is where commercially available wearables offer unique advantages.

Limitations

All children were instructed to wear the bracelet during waking hours without interruption. However, in certain sports it is forbidden to wear a wrist bracelet (i.e. contact sports) and therefore it is possible that such intense activities were not captured.

Children and parents alike reported the herein used wearable as an exciting new toy, the positive acceptance and feedback of the wearable has already been reported [93]. Therefore, it could be suggested that objective measured PA is likely to be over-reported and lower in reality. As this is most likely true for both, children with CHD and healthy children, comparison between the groups should not be biased.

In terms of subjective PA estimation in children our study does not include caregivers, who are mainly responsible for their children's lifestyle especially at a younger age. For future studies evaluating subjective PA estimation, the parents' estimation could provide other important findings.

Like other studies [122,155] we applied the »soft« WHO criteria for MVPA as a weekly average. The much harder variant to interpret the criteria is ≥60 minutes of PA on every single day. Then only 27.9% of the CHD and 40.6% of the healthy peers fulfill them. However, since it has been shown that every minute of MVPA is beneficial [108] this article focuses more on MVPA minutes and not on threshold levels. Especially because there is no clearly defined daily step goals for children to analyze the measured step count against.

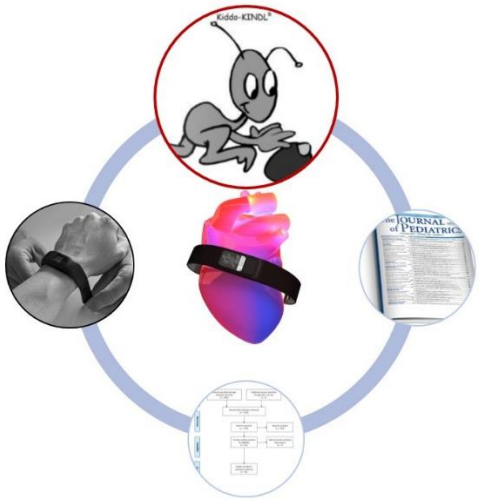
Conclusion

This cohort of children with various CHD was quite active in general. Nevertheless, MVPA needs to be promoted in overweight or obese patients, with complex CHD severity, and in particular in those with total cavopulmonary connection. Subjective estimation of daily MVPA is fairly correct in only about half of all children with CHD thereby failing to draw an accurate picture on these patients' activity. This underlines the importance of objective and reliable measures in clinical pediatric settings.

3.4 Discussion of Publication II

In the above-mentioned analysis, the cohort of children with various CHD was quite active in general, and pretty much as active as healthy peers. These findings are quite pleasant since it shows that – at least in the specialized center of the German Heart Center Munich– the encouragement towards a physically active lifestyle seems to be somewhat successful in young patients. Derivative of these findings is the idea that clinicians and medical professionals could learn from this cohort to find out what makes these children so active. One explanation might be that these children have a high level of disease and physical awareness. Furthermore, they are in routine medical care on a yearly basis. Thereby, they might become even more aware of how important a healthy lifestyle is in their specific case.

In analysis, a discrepancy was found between the »hard« WHO criteria i.e. reaching 60 minutes of MVPA every single day, and the »soft« WHO criteria i.e. reaching 60 minutes of MVPA per day on average. Since the publication of this study, the WHO has published updated *»2020 Guidelines on Physical Activity and Sedentary Behavior«* [26]. In these guidelines, the PA recommendation is a bit vaguer than it was previously stating that »*Children and adolescents should do at least an average of 60 minutes per day of moderate-to-vigorous-intensity, mostly aerobic, physical activity* ***across the week****«.* This phrasing gives some more room for interpretation whether the »hard« or »soft« criteria is the correct application of these guidelines. Since every minute of PA seems to be beneficial, application of the soft WHO criteria seems to be appropriate. Eventually, some PA is better than none.



The cohort size of the previous study was quite good. After a couple of years of more research on this cohort, the analysis was expanded to a more detailed look, especially on Quality of Life. Therefore, in the next study, the focus was not on the PA of our young patients but in more detail aimed to determine whether there is an association between objectively assessed PA and HRQoL in children with CHD. Within the ongoing project at the German Heart Center Munich the sample size was expanded to almost 350 children who were equipped with our PA tracking devices. On top of that, all these children completed an elaborate questionnaire assessing health-related quality of life with the goal of associating both parameters. The goal was to determine whether there is a translation of PA into better Quality of Life.

3.5 Move more – be happier? Physical Activity and Health-Related Quality of Life in Pediatric Patients with Congenital Heart Disease

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Conflicts of interest:

No conflict of interest. No competing interests for any of the authors.

Individual contribution:

The PhD candidate Leon Brudy is the principal author of this paper. Along with Michael Meyer he sampled the data at the German Heart Center Munich. Leon Brudy also statistically analyzed the data, presented the results, and drafted the manuscript, all under supervision of Jan Müller. Jan Müller, Renate Oberhoffer, and Peter Ewert all valuable input for further improvement of the manuscript. All authors have read and approved the final version of the manuscript. Leon Brudy also handled the submission process.

Abstract

Objective: This study aimed to determine whether there is an association between objectively assessed physical activity (PA) and health-related quality of life (HRQoL) in children with CHD.

Patients and Methods: From September 2017 to January 2021, 343 children with CHD (12.1 ± 3.3 years, 135 girls) provided valid PA data after a 7-day objective PA assessment. PA was evaluated as average daily steps and moderate-to-vigorous physical activity (MVPA) minutes assessed via wearable bracelet Garmin vivofit® Jr. These children also completed the KINDL® - a 24 Likert-scaled item questionnaire assessing HRQoL in the six dimensions physical well-being, emotional well-being, self-esteem, family, friends and everyday functioning.

Results: Daily Steps (r=.166, p=.003) and daily MVPA minutes (r=.134, p=.017,) were both correlated to total KINDL® score. Furthermore, both steps and MVPA were associated with the subscales physical well-being (steps: r=.165 p=.003; MVPA: r=.129, p=.022), friends (steps: r=.210, p<.001, MVPA: r=.179, p=.001). Steps were also associated to everyday functioning (r=.142, p=.012). Logistic regression showed each MVPA minute increase conferred to a 1% increase in reporting better HRQoL (OR: 1.009 [95% CI: 1.002 - 1.017]), p=.019).

Conclusions: PA was positively associated with HRQoL in children with CHD. Patients who move more are more likely to report better HRQoL. Continuous encouragement towards more PA seems to be crucial in a holistic approach to medical aftercare in children with CHD.

Introduction

With increasing survival rates, a multidimensional approach to health becomes more important to improve long-term outcome in patients with congenital heart disease (CHD) [98]. Thereby, the goal is to enhance patient care and improve patients' lives. Physical Activity (PA) and a physically active lifestyle are one key component in this endeavor. Recent studies using objective measures showed children with CHD to be almost as active as healthy peers [123,170], and the positive impact of PA on optimal physical and mental well-being is widely established [50].

Mental health in the form of Health-related quality of life (HRQoL) has been studied extensively in pediatric patients with CHD. The findings, however, are quite mixed. While some studies find HRQoL in children with CHD to be worse than healthy peers and increasingly worse with higher CHD complexity [53], others find only physical subscales of

HRQoL to be reduced [54], or HRQoL to be normal [171] or even better in children with CHD than in healthy [55].

To date, three studies with just relatively small sample size have aimed to associate PA and HRQoL in pediatric patients with CHD. Two studies used subjective measures in the form of questionnaires to assess PA and found a positive correlation to HRQoL [60,62]. Only one study used an objective measure in the form of a waist-worn accelerometer, and also found greater PA to be associated with better HRQoL [61]. As subjective measures of PA lack objectivity [172], wearable physical activity trackers have previously been established as a useful tool to assess PA in patients with CHD [170]. Therefore, this study used commercially available PA trackers in a large cohort of children with CHD. The aim was to determine whether there is an association between objectively assessed PA and HRQoL in children with CHD.

Participants and Methods

Within the ongoing cardiovascular screening study FOOTLOOSE (German Clinical Trials Register ID: DRKS00018853) at the outpatient clinic of the German Heart Center Munich, 343 children with CHD (12.1 ± 3.3 years, age-range: 5.9 – 18.3 years, 135 girls) provided valid PA data after a 7-day objective physical activity assessment from September 2017 to January 2021. These children also completed the KINDL® questionnaire for assessment of HRQoL.

All patients were free of acute infections and in good general health without sport or exercise restrictions. Exclusion criteria were neurological diseases, cognitive retardation, or surgical or catheter intervention within the last six months. According to ACC criteria [19], CHD severity was distributed as follows: 162 complex, 109 moderate, 64 simple. For five patients with arrhythmia and three patients with Marfan Syndrome severity class could not be defined. 86 patients were native CHD, 257 surgically corrected CHD. Complete cohort description can be accessed in Table 13.

After being provided with information about the study protocol, all children and their legal guardians gave written informed consent. The study was conducted in accordance with the declaration of Helsinki (revised 2008) and approved by the local ethical board of the Technical University of Munich (project number: 314/14). Previous results out of this study were recently published [123].

Table 13: Study Subjects

	n	Sex (female) n (%)	Age Mean ± SD	BMI z-score Mean ± SD	Steps Mean ± SD	MVPA Mean ± SD
CHD	343	135 (40.0%)	12.1 ± 3.3	- 0.30 ± 1.2	9490 ± 3120	83.6 ± 28.7
CHD Diagnosis						
Left Heart Obstruction	66	20 (30.0%)	12.2 ± 3.3	-0.51 ± 1.2	10120 ± 3321	90.1 ± 29.8
Right heart Obstruction	86	33 (38.4%)	11.9 ± 3.1	-0-38 ± 1.4	9150 ± 3106	76.4 ± 29.6
Isolated Shunts	54	29 (53.7%)	12.3 ± 3.5	-0.05 ± 1.0	9312 ± 2943	84.1 ± 26.1
TGA after Switch	37	9 (24.3%)	11.9 ± 3.1	-0.09 ± 1.0	11269 ± 3508	99.0 ± 29.8
TCPC	55	18 (32.7%)	13.2 ± 3.4	-0.17 ± 1.0	9169 ± 2704	82.0 ± 27.0
Miscellaneous	45	26 (57.8%)	11.4 ± 3.6	-0.43 ± 1.3	8403 ± 2558	76.8 ± 23.5
CHD severity*						
Simple	64	29 (45%)	12.4 ± 3.6	-0.09 ± 1.1	9698 ± 3025	85.5 ± 27.5
Moderate	109	43 (39%)	11.6 ± 3.1	-0.36 ± 1.2	9460 ± 3225	81.4 ± 29.1
Complex	162	60 (37%)	12.4 ± 3.4	-0-34 ± 1.3	9561 ± 3102	85.3 ± 29.2
Surgical Status						
Native CHD	86	35 (40.7%)	11.5 ± 3.3	-0.30 ± 1.1	9574 ± 3136	83.2 ± 30.3
Surgically corrected CHD	257	100 (38.9%)	12.4 ± 3.3	-0.29 ± 1.2	9462 ± 3121	83.8 ± 28.2

*for 5 patients with arrhythmia and 3 with Marfan Syndrome severity class could not be defined, CHD: congenital heart disease, TGA: Transposition of the Great Arteries, TCPC: Total Cavopulmonary Connection, BMI: Body Mass Index, MVPA: Moderate-to-vigorous Physical Activity

PA was evaluated as average daily steps and average daily moderate-to-vigorous physical activity (MVPA) minutes measured via wearable bracelet Garmin vivofit Jr. ® (Garmin Ltd. Olathe, KS, USA) for seven consecutive days. This is a wearable specifically designed for children, which tracks PA in steps and every single MVPA minute throughout the day. All children were instructed to wear the bracelet during all their waking hours including when showering, swimming, leisure time and organized sports, with possible removal overnight. These commercially available physical activity trackers have been validated against gold standards of PA assessment [79,80], and have previously been used in various pediatric research setting [123,173].

Health-related Quality of Life

HRQoL was assessed via KINDL® - a 24 Likert-scaled item questionnaire referring to the past week in six subscales: physical well-being, emotional well-being, self-esteem, family, friends and everyday functioning. Each dimension contains four questions and asks the children to score their answers on a 5-point Likert scale (never, seldom, sometimes, often, always). These items then generate a total HRQoL score, and also provide individual scores for the six subcategories. Separate versions for patients younger (Kid-KINDL®) and older than 14 years (KiddoKINDL®) were used. The complete questionnaire can be accessed elsewhere [67]. The KINDL® questionnaire has been recognized as a common, internationally standardized tool in assessing HRQoL [44] and has been shown to be adequate in measuring HRQoL in children with [55] and without [174] CHD.

Data analyses

KINDL® questionnaire answers were transferred to a score ranging from 0-100 and analyzed as a total score as well as in the separate subscales. Higher scores indicate better HRQoL. Regarding PA data, steps and MVPA minutes for every day were analyzed and also computed to a weekly average according to current World Health Organization (WHO) criteria [35]. Data was valid if at least three weekdays and one weekend day (four days in total) were present allowing for weekly average. Just like previous studies on the topic we defined meeting the WHO guidelines as mean daily MVPA ≥60 min per day [122,123], thereby applying the “soft” WHO criteria for MVPA as a weekly average. Interpreting the criteria as ≥60 minutes of PA on every single day is a much harder variant, and since it has been shown that every minute of MVPA is beneficial [108] this article focuses more on MVPA minutes and not on threshold levels.

Partial Correlation controlling for sex was used to determine possible associations between PA and HRQoL. As both PA and HRQoL are known to decline with age we chose to not control for age in the analysis due to the collinearity to both parameters. Logistic regression was calculated to associate likelihood of better HRQoL based on daily PA in the form of MVPA minutes. A KINDL® total score of 80 was used as a cut-off into better and worse HRQoL as this represents the Median value of the cohort.

All data are shown in mean ± standard deviation (SD). The effect sizes 'r' were interpreted according to Cohen [175]. All data were analyzed using SPSS 25.0 software (IBM Inc., Armonk, NY, USA) with a two-tailed level of significance at p-value ≤ .05.

Results

On a weekly average, children with CHD accumulated 9,490 ± 3,120 daily steps and 83.6 ± 28.7 daily MVPA minutes. Girls with CHD achieved significantly fewer daily MVPA minutes (79.8 ± 27.8 vs. 86.2 ± 29.1, p=.044) than boys with CHD. Applying the soft WHO criteria, 268 children with CHD (78%) reached at least an average of 60 MVPA minutes per day. Considering the harder WHO criteria, 94 children with CHD (27%) achieved 60 MVPA minutes every single day of the week. Total KINDL® score was 78.1 ± 10.2, subscales are further described in Table 14.

Table 14: Cohort Description of mean daily PA and mean HRQoL

Daily Steps	
Whole week (mean)	9490 ± 3120
Monday-Friday (mean)	9904 ± 3258
Weekend (mean)	8449 ± 3863
Daily minutes of MVPA	
Whole week (mean)	83.6 ± 28.7
Monday-Friday (mean)	86.9 ± 29.5
Weekend (mean)	75.5 ± 34.9
HRQoL	
Total KINDL® score	78.3 ± 10.2
Physical well-being	78.1 ± 17.0
Emotional well-being	82.1 ± 12.6
Self-esteem	69.7 ± 18.1
Family	85.3 ± 13.5
Friends	79.3 ± 16.1
Everyday functioning	74.8 ± 17.3

CHD: congenital heart disease, MVPA: moderate-to-vigorous physical activity, HRQoL: Health-related Quality of Life, MVPA: moderate-to-vigorous physical activity

After controlling for sex, daily Steps (r=.166, p=.003) and daily MVPA minutes (r=.134, p=.017,Figure 17) were both positive correlated to total KINDL® score. In more detail, daily steps were also associated with the subscales physical well-being (r=.165 p=.003), friends (r=.210, p<.001), and everyday functioning (r=.142, p=.012), while average daily MVPA minutes were correlated to the subscales physical well-being (r=.129, p=.022) and friends (r=.179, p=.001) (Figure 18).

Logistic regression was found to associate HRQoL based on daily PA in the form of MVPA minutes (OR: 1.009 [95% CI: 1.002 - 1.017]), p=.019). Each MVPA minutes increase conferred to a 1% increase in reporting a better HRQoL as measured with the total KINDL® score above 80.

Figure 17: Association of Moderate-Vigorous Physical Activity and Total KINDL® score

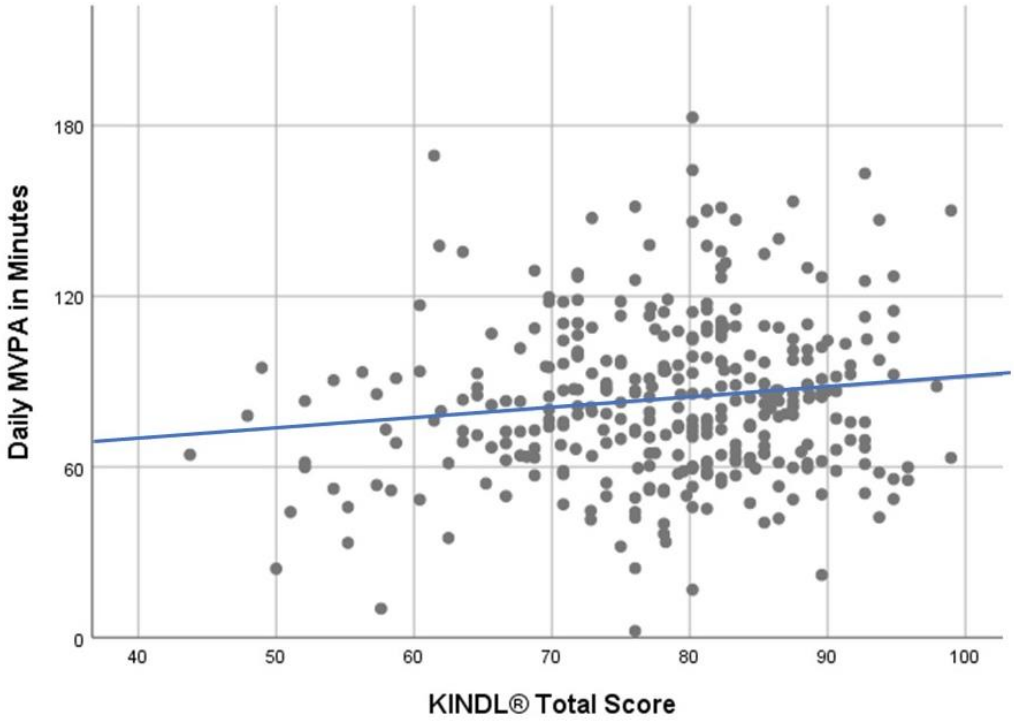
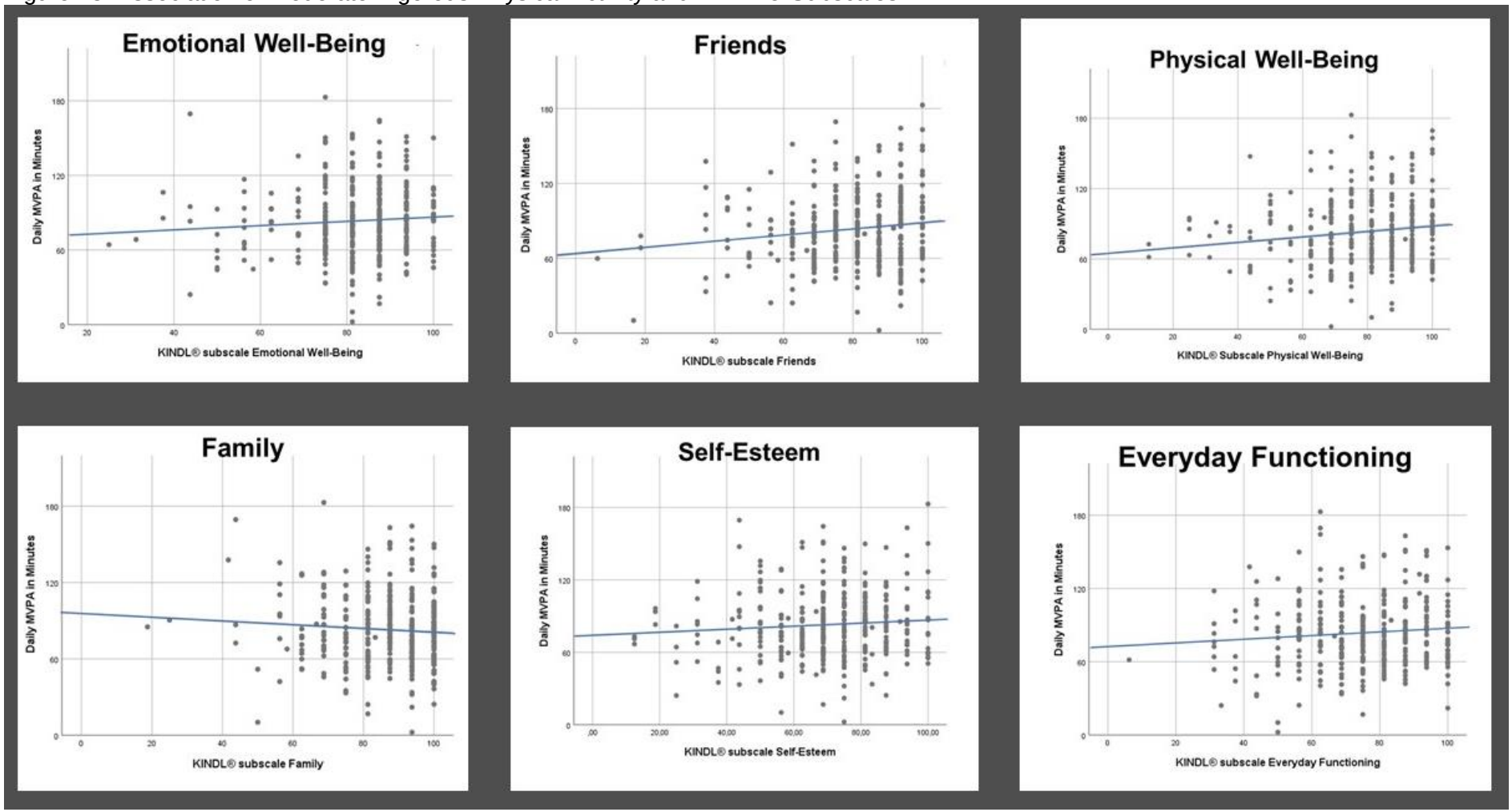


Figure 18: Association of Moderate-Vigorous Physical Activity and KINDL® Subscales



Discussion

In this analysis an association between daily PA and HRQoL, as well as its subscales physical well-being, friends, and everyday functioning was found. In more detail, the study outlined that children with CHD who move more appear to report better HRQoL with a 1% increase in HRQoL with every one minute of more MVPA. Or put differently, children with CHD who move more, are happier.

Our findings in children with CHD are in line with two previous studies on exercise capacity, PA, and HRQoL in adult patients with CHD (ACHD). Kröönström and colleagues recently found a correlation between exercise capacity and the physical function domain of the Short Form-36 (SF-36) assessing HRQoL in 747 ACHD [176]. Müller et al. showed a lower probability for reduced HRQoL in physically active patients compared to inactive patients in 786 ACHD [63]. However, our findings are in contrast to those of an systematic review covering literature from the first decade of the century which found that PA was rarely associated with physical or psychosocial domains of HRQoL [177]. While PA assessment was subjective in the majority of the included studies, our PA data was gathered via objective wearable devices. Furthermore, within the last decade medical aftercare has shifted even more towards a liberal approach to recommending PA than it was the case in the early 2000s. Therefore, the findings of the former mentioned systematic review [177] and our study need to be compared with caution.

The association of PA and the subscales of friends and everyday functioning indicate that a physically active lifestyle is closely intertwined with social aspects of daily life. In fact, the connection between movement in childhood and social skills has previously been made in the general pediatric population [178], and can now also be established in children with CHD. Those patients who are more physically active might also be fitter [125,179], and as a result are better able to keep up with their peers. This could be an explanation why PA is associated with subscales friends and everyday functioning in our study. On the contrary, patients with CHD are born with their congenital defect and therefore grow up perceiving their situation as normal and health status independent of HRQoL [180,181]. This might be a reason why the subscales with more of an internal locus of control such as emotional well-being, self-esteem, or family might not be affected in the association to PA in our analysis.

A previously published study out of our institution specifically evaluated HRQoL alongside health-related physical fitness (HRPF) in children with isolated left-to-right shunts

[171]. It found HRQoL to be normal, but HRPF to be reduced. Considering these findings alongside with our results on PA being associated with HRQoL, PA interventions in patients with CHD are worth to consider. In fact, there have already been some studies on aiming to improve PA in patients with CHD [182]. While all studies found PA interventions in patients with CHD to be safe, there is still insufficient evidence to definitively determine the impact of physical activity in patients with CHD, and more interventional work is needed.

As previously mentioned, findings on HRQoL in children with CHD are mixed, with some reporting lower, similar, or better levels than otherwise healthy children (5-8). In ACHD, the HRQoL seems to generally be worse than healthy, and worse in older patients and patients with more complex CHD [56-59]. Along with the fact that PA decreases with increasing age in healthy [2] and adults with CHD [170], and the findings of this study – that PA and HRQoL seem to go hand in hand in children with CHD – it becomes even more imperative to continuously encourage patients with CHD to be physically active.

While the effect sizes correspond to a small effect according to Cohen [175] it is imperative to consider that the study is following an active cohort of patients with CHD. Almost 80% of the patients in this study did reach the WHO recommendations on PA. In global perspective, 80% of children and adolescents do not reach this recommendation [35]. It seems that in our specialized center (just as in many others across Europe), patients are being encouraged to be quite active. With just very few exceptions, almost all patients with CHD are encouraged to reach regular PA recommendations of the general population as it is safe and beneficial [10]. However, considering its association to HRQoL, patients with CHD need to continuously be encouraged to follow an active lifestyle. Furthermore, when applying the “hard” WHO criteria of reaching at least 60 minutes MVPA every single day, only 27% of our cohort are sufficiently active every single day. This encouragement is especially important in the context of PA habituality. Active children will most likely become active adults [38]. Along similar lines, our findings suggest that active children with CHD are more likely to be happy children.

Limitations

We acknowledge that a healthy reference cohort would have further benefited our analysis, especially since children and parents alike refer to the wearable as an exciting tool. PA might be overrepresented considering the Hawthorne Effect [74]. Furthermore, certain

organized sports forbid to wear wrist bracelets. Therefore, intense activities might not be fully included.

Conclusion

This study found that PA was positively associated with HRQoL in children with CHD. Pediatric patients who move more are more likely to report better HRQoL. Considering other impairments beyond cardiac issues is fundamental in aftercare of patients with CHD. Continuously encouraging patients with CHD seems thereby to be crucial, also for better HRQoL.

3.6 Discussion of Publication III

In this previous publication the analysis not only confirmed that this is quite active of a cohort of pediatric patients with CHD, but also found an association between a physically active lifestyle and aspects of mental health in the form of HRQoL. The more these children move, the more likely they are to feel better, be happier. This is especially interesting in the context of the earlier mentioned application of »hard« or »soft« WHO criteria and the benefits of any kind of PA. With a translation of more PA into a higher likelihood of having better HRQoL the encouragement to reach any levels of PA is crucial. Furthermore, this previous publication opens new research trajectories with an expansion the parents of children with CHD. As parents of chronically ill children are susceptible to increased stress [183], it could be interesting to determine whether parents of active children are also happier parents.

The finding of an active cohort is also especially interesting, because generally children are not sufficiently active enough worldwide. In fact, 80% of children and adolescents are not getting enough movement on a daily basis. Interestingly, in our cohort, the results are quite contrary. Almost 80% of these children are moving enough on a daily basis. Thereby, several questions arise: Why might that be the case? Are there specific reasons why these children are so active? And if so, is there a way to apply these reasons to other settings and cohorts? Before going into more of a discussion on future research steps, the next and last publication of this dissertation expands the view of PA behavior to adult patients with CHD.

The set-up was similar as in the pediatric study. However, instead of *the Garmin vivofit jr.*, the *Garmin vivofit 3* device for adults was used. The question determining subjectively estimated PA was slightly altered to fit current WHO guidelines for adults. And this time, the comparison to healthy was expanded to also cover whether healthy can estimate how active they are. The findings of the following study are intriguing, especially because they appear quite different than the previous promising findings of our younger patients.

3.7 Adults with Congenital Heart Disease move well, but lack intensity: A Cross-Sectional Study Using Wrist-Worn Physical Activity Tracker

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The PhD candidate Leon Brudy is the principal author of this paper. Together with the Co-author Anna-Luisa Häcker he sampled the data in the study center. Leon Brudy analyzed the data and drafted the manuscript and presented the results. Jan Müller was responsible for conception and supervision of the study design and revised the manuscript. Michael Meyer, Alfred Hager, Renate Oberhoffer und Peter Ewert all gave important input to improve the manuscript. All authors have read and approved the final version of the manuscript. Under supervision of Jan Müller, Leon Brudy handled the submission process.

Abstract

Objective: This study compared objectively measured and self-reported physical activity (PA) in adults with congenital heart disease (ACHD) to a healthy reference cohort (RC).
Patients and Methods: From May 2017 to August 2020, 211 ACHD (39.9 ± 9.7 years, 101 female) and 141 healthy adults (35.9 ± 14.7 years, 76 female) participated in a wearable-based and self-reported PA assessment. Moderate-to-vigorous physical activity (MVPA) and step-count were recorded with Garmin vivofit®3 for seven consecutive days. Additionally, subjects were asked to report the number of days they are active for ≥ 30 minutes throughout the week.
Results: Only 33 (17%) ACHD and 36 (26%) healthy controls (p=.030) accumulated the World Health Organization's (WHO) recommendation of 150 minutes MVPA per week. ACHD were less active per week (ACHD: 40.0 [0.0; 101.0] min. MVPA vs. RC: 75.0 [22.5; 152.5] min. MVPA, p=.002) and walked fewer daily steps (ACHD: 8246 [6505; 10434] vs. RC: 9413 [7621; 11654], p=.001) than healthy controls. Especially patients with moderate (p=.030), complex (p<.001), or surgically corrected (p=.008) CHD accumulated significantly less MVPA than healthy peers throughout the week. A large majority of 72% of ACHD and 58% of RC overestimated their weekly active days by more than one day.
Conclusions: ACHD walked quite a few steps daily but lacked intensity. ACHD were less active than healthy controls and failed to reach international recommendations. They therefore need encouragement towards more intense movement to improve exercise capacity and lower cardiovascular risk. Self-reported PA showed no agreement to the objectively measured PA.

Introduction

With its benefits of reducing health risks and preventing chronic diseases physical activity (PA) could be considered a cure-all for a lot of chronic current health problems. Aside from prevention of cardiovascular disease, several cancer types, type 2 Diabetes, regular PA also improves quality of life, memory and brain function, and decreases mortality [4,51,184].

Encouragement of a physically active lifestyle and regular sports participation have become imperative in pursuit of a preventative approach in routine medical follow-ups of patients with congenital heart disease (CHD) [185]. PA is known to be beneficial for long-term cardiovascular health, without additional risks for almost all patients with CHD [10]. Especially due to the preventative nature of regular physical activity [2] this is a crucial

topic in the context of an ageing CHD cohort.

PA behavior can either be assessed by patients' self-report or objectively through researchers or clinical professionals. Self-report is fast and convenient [25,186] but might fail to be accurate [128]. Objective assessment offers the advantage of suffering less personal bias and more accuracy, but also requires more equipment and time [25]. Objective PA in patients with CHD has been assessed in a number of studies previously, both in children [61,117-121,123,187] and in adults [124-128]. Children with CHD are found to mostly be quite active. In adults with CHD (ACHD) the picture is a bit more unclear. It generally seems as previous studies found [188] ACHD to be similarly active as a healthy reference cohort but failing to reach official PA guidelines. However, the majority of studies is older with relatively small sample size. Therefore, no clear answer about how active ACHD really are can currently be given [188].

This study aimed to compare PA in adults with congenital heart disease (ACHD) to a healthy reference cohort (RC), and further evaluate the agreement of self-reported and objectively measured PA.

Patients and Methods

From May 2017 to August 2020, 211 ACHD (39.9 ± 9.7 years, 101 female) participated in an ongoing cardiovascular screening study (German Clinical Trials Register ID: DRKS00015248) during their routine outpatient visit at the German Heart Center Munich. As part of this study, participants were equipped with wearable devices measuring PA and reported about their activity status. Twenty-three patients had aortic stenosis, 19 coarctation of the aorta, 38 isolated shunts, 52 Tetralogy of Fallot or pulmonary stenosis, 24 transposition of the great arteries, 13 Fontan circulation and 42 miscellaneous CHD. According to ACC criteria [19] 99 patients were of complex CHD severity, 82 moderate, and 25 simple. For 5 patients CHD severity could not be defined. 147 had at least one open-heart surgery, 64 had native conditions or at least no open-heart surgery. For comparison 141 healthy adults (35.9 ± 14.7 years, 76 female) were additionally recruited from several projects in and around the German Heart Center Munich from November 2017 to August 2020. Anthropometric of study subjects is described in Table 15.
All participants were free of neurological diseases or acute infections, without sport restrictions, and gave written informed consent after being provided with the study protocol. The study was designed in accordance with the declaration of Helsinki (revised 2008) and approved by the local ethical board of the Technical University of Munich (project number 64/17S).

Table 15 : Study Subjects

	n	Sex (female) n (%)	Age Mean ± SD	BMI Mean ± SD
ACHD	211	101 (48%)	39.9 ± 9.7	24.9 ± 4.0
RC	141	76 (54%)	35.9 ± 14.7	23.3 ± 3.2
p-value*	-	.279	**.002**	**<.001**
Diagnostic Subgroups				
AS	23	5 (22%)	40.4 ± 11.3	25.5 ± 3.5
CoA	19	5 (26%)	39.3 ± 6.1	25.1 ± 3.9
Isolated Shunts	38	24 (63%)	44.0 ± 10.6	25.5 ± 4.5
ToF	52	28 (54%)	40.3 ± 7.8	24.7 ± 4.6
TGA	24	9 (38%)	37.7 ± 4.0	25.2 ± 3.3
Fontan	13	6 (46%)	36.9 ± 7.7	24.6 ± 3.1
Miscellaneous	42	24 (57%)	39.8 ± 11.4	24.6 ± 3.8
CHD Severity				
Simple	25	10 (40%)	46.7 ± 12.5	26.1 ± 3.9
Moderate	82	41 (50%)	40.1 ± 8.4	25.2 ± 4.5
Complex	99	46 (47%)	38.8 ± 8.3	24.6 ± 3.4
Not defined	5	4 (80%)	26.5 ± 17.7	23.2 ± 5.7
OP Status				
Native CHD	64	30 (47%)	40.54 ± 12.0	25.6 ± 4.3
Surgically corrected	147	71 (48%)	39.7 ± 8.5	24.7 ± 3.8

*significant with p<.05, T-test comparing ACHD to RC, ACHD: adults with congenital heart disease, RC: reference cohort, AS: Aortic Stenosis, CoA: Coarctation of the Aorta, ToF: Tetralogy of Fallot, TGA: Transposition of the Great Arteries, EBS: Ebstein Anomaly, TGA: Transposition of the Great Arteries, SD: standard deviation, CHD: congenital heart disease

All participants were instructed to wear a Garmin vivofit® 3 (Garmin Ltd. Olathe, KS, USA) wrist-bracelet for seven consecutive days starting one day after they received the device during all waking hours with possible removal overnight. The device is waterproof and tracks PA in active minutes and steps. As part of the built-in algorithm, the device assesses moderate or vigorous physical activity (MVPA) only if bouts of at least 10 minutes are reached – which is in line with current WHO recommendations for PA [35].

PA data had to include at least three weekdays and one weekend (four days in total) to be considered valid and put into the statistical analysis. 199 participants had complete and valid reports for objective PA on seven consecutive days. 12 (6%) participants had incomplete data but at least four valid days including one weekend day and three weekdays. Before receiving the wearable device, all participants were asked to subjectively estimate their days of activity (»On how many days of an average week are you active for at least 30 minutes per day?«) on a Likert scale from none to seven. This subjective self-report was then directly compared to the objective assessment.

Physical Activity Guidelines

Steps were analyzed for every day and MVPA minutes for weekly total according to current WHO criteria [35]. Currently the WHO recommends the following levels of physical activity for adults aged 18-64 years per week: at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of the both with aerobic activity in bouts of at least 10 minutes [35].

Data analyses

All descriptive data are expressed as mean ± standard deviation (SD). As many of our participants have accumulated almost no MVPA minutes due to the hard WHO criteria of bouts of 10 minutes [35], the data is skewed towards the lower end. Therefore, we decided to use non-parametric tests for group comparison to avoid large standard deviations in display. Hence, comparison of the primary outcomes MVPA and steps between CHD and RC was analyzed via non-parametric Mann-Whitney-U-Test and Kruskal-Wallis-Test and data is expressed as median with interquartile range. Intraclass Correlation Coefficient (ICC) compared subjectively reported with objectively measured PA.
All data were analyzed using SPSS 25.0 software (IBM Inc., Armonk, NY, USA) with a two-tailed level of significance at p-value ≤ .05. Figures were drawn using R Studio and the package ggplot2 (RStudio Team. RStudio: Integrated development for R. Boston: RStudio, Inc. 2015.).

Results

A large majority of both groups failed to reach WHO recommendation of 150 minutes MVPA per week. Even fewer ACHD (n=33, 17%) than RC (n=36, 26%, p=.030) accumulated the recommended amount of MVPA minutes.

Overall, ACHD accumulated less MVPA (ACHD: 40.0 [0.0; 101.0] MVPA min vs. RC: 75.0 [22.5; 152.5] MVPA min, p=.002) and walked fewer steps (ACHD: 8246 [6505; 10434] vs. RC 9413 [7621; 11654], p=.001) than healthy controls. This significant difference in MVPA and steps remains when evaluating weekdays and weekend days separately (Table 16).

Table 16: Comparison of daily steps and weekly moderate or vigorous activity (MVPA) in adults with congenital heart disease (ACHD) vs. healthy controls (RC), split into weekdays and weekend

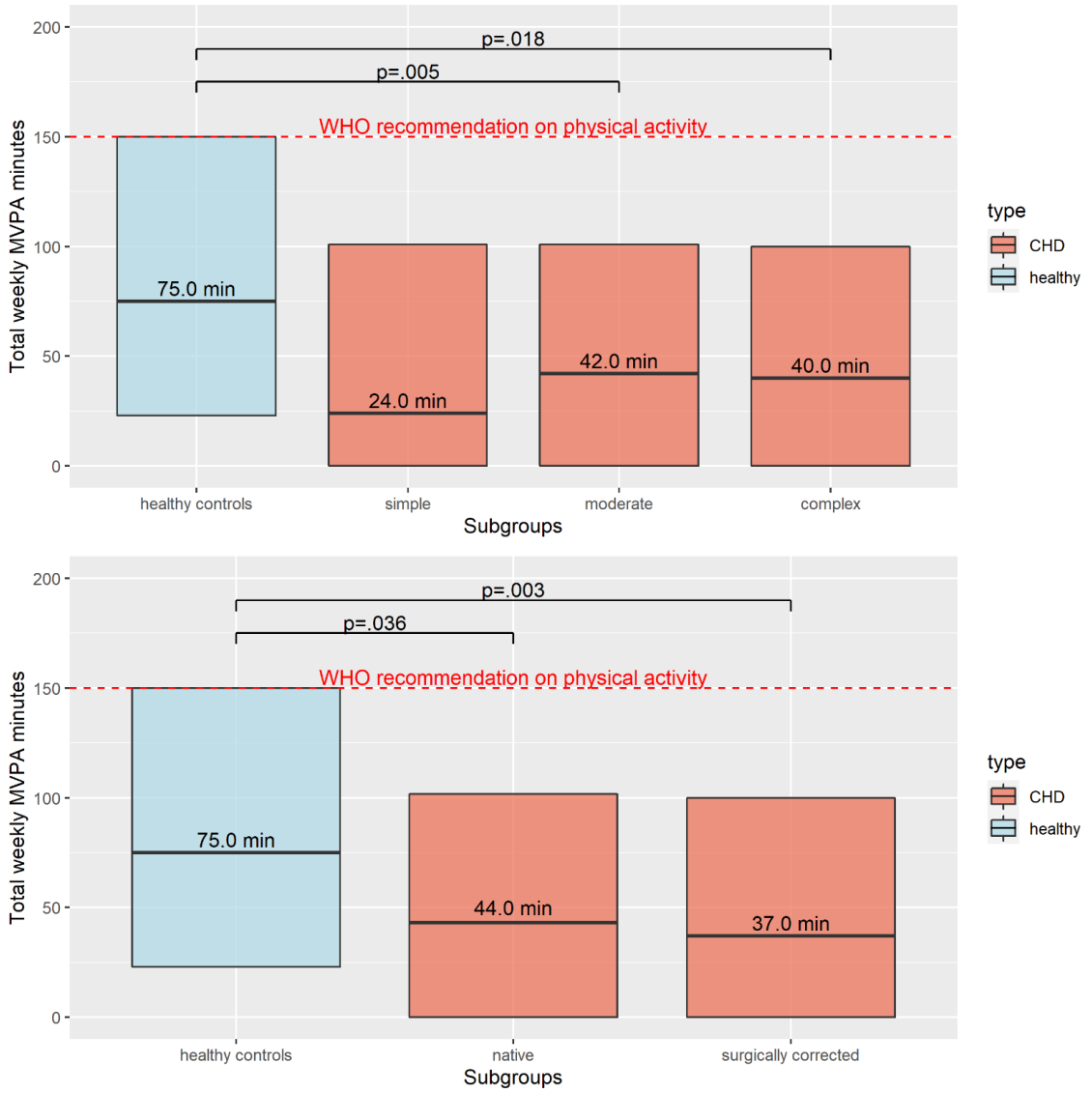
Daily Steps			
	ACHD (n=211) Median [IQR]	**RC (n=141) Median [IQR]**	**p-value***
Whole week (mean)	8246 [6505; 10434]	9413 [7621; 11654]	**.001**
Monday-Friday (mean)	8650 [6386; 10933]	9625 [7516; 11647]	**.003**
Weekend (mean)	8034 [5344; 10406]	5845 [6598; 11957]	**.007**
Weekly MVPA			
	ACHD (n=199) Median [IQR]	**RC(n=141) Median [IQR]**	**p-value***
Whole week (total)	40.0 [0.0; 101.0]	75.0 [22.5; 152.5]	**.002**
Monday-Friday (mean)	4.7 [0.0; 14.5]	10.0 [1.0; 19.3]	**.002**
Weekend (mean)	0.0 [0.0; 18.3]	8.5 [0.0; 25.5]	**.018**

Mann-Whitney-U-Test comparing ACHD with RC, *significant with p<.05; ACHD: adults with congenital heart disease, RC: reference cohort, MVPA: moderate-to-vigorous physical activity, IQR: Interquartile range

Subgroup analysis

When split by surgical status (Figure 19), both native and surgically corrected CHD reached less total weekly MVPA (operated ACHD: 37.0 [0.0; 100.0] MVPA min vs. RC 75.0 [22.5; 152.5] MVPA min, p=.008, Figure 19) and walked fewer daily steps (operated ACHD: 8206 [6306; 10625] vs RC: 9413 [7621; 11654], p=.004) than healthy controls. Regarding CHD severity, moderate and complex CHD accumulated less total weekly MVPA (ACHD: 42.0 [0.0; 101.5] MVPA min vs. RC: 75.0 [22.5; 152.5] MVPA min, p=.030, Figure 19) while complex CHD walked fewer daily steps (ACHD: 7801 [6227; 10209] vs. RC: 9413 [7621; 11654], p<.001) than healthy controls. Diagnostic CHD Subgroup analysis revealed no significant differences (Kruskal Wallis test, p=.151).

Figure 19: Comparison of total weekly moderate or vigorous physical activity (MVPA) between healthy controls and adults with congenital heart disease according to their complexity and surgical status



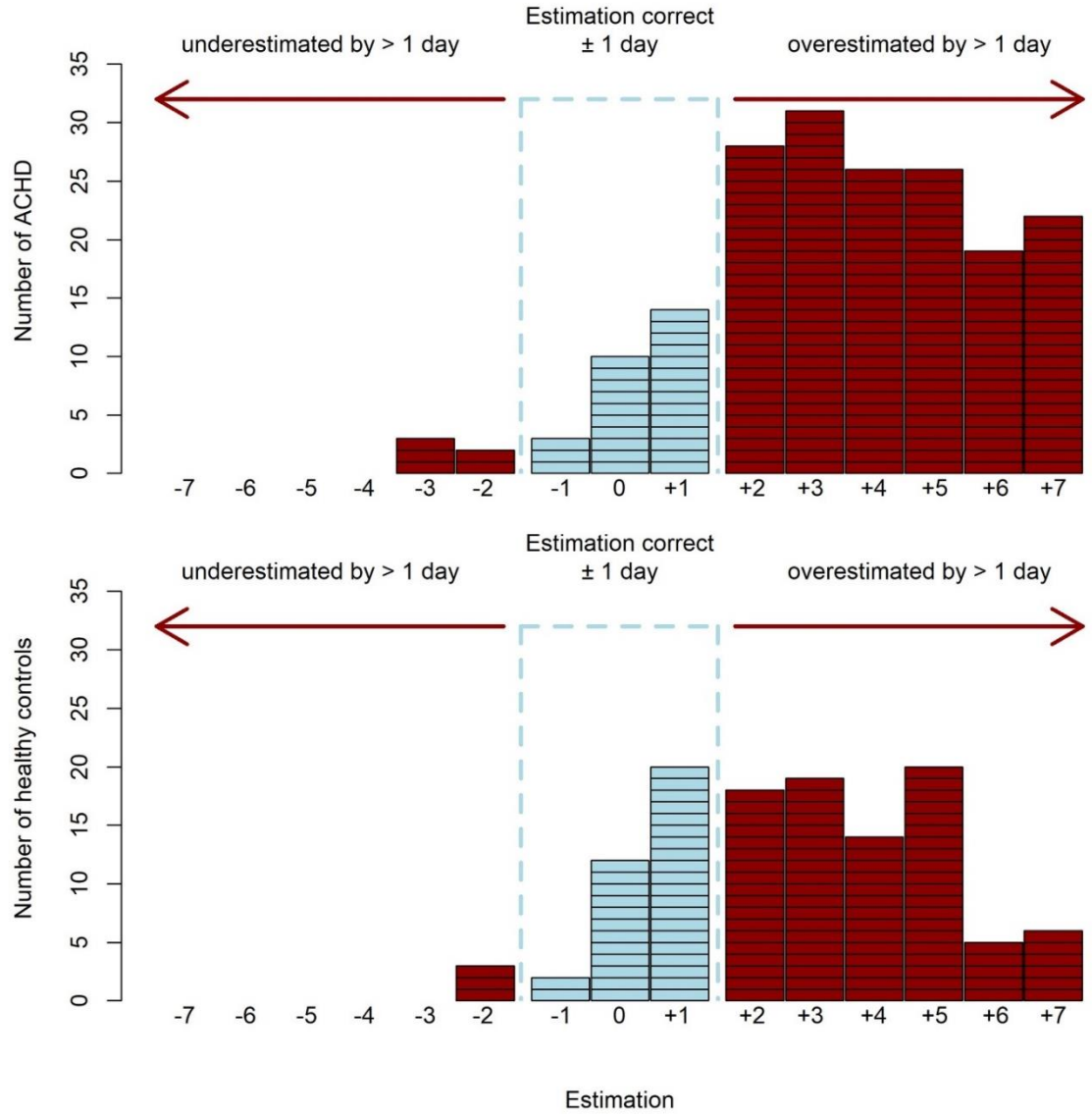
Subjective vs. objective PA

184 ACHD and 119 healthy controls had valid data for both subjective and objective PA assessments. When asked about the number of days of an average week they are active for at least 30 minutes per day ACHD subjectively reported to be active on 4.6 ± 1.9, and RC on 4.3 ± 1.9 days per week. Objective PA measurements via the wearable revealed ACHD to reach 30 or more minutes of MVPA on 1.1 ± 1.6 days of the week, and RC on 1.5 ± 1.8 days of the week.

When comparing subjective with objective PA assessment, 27 (13%) ACHD estimated their days of reaching 30 or more minutes of PA correct or were off by just one day, while 152 (72%) overestimated and 5 (2%) underestimated their daily PA by more than one

day. In RC, 34 (24%) estimated correctly or were off by one day, 82 (58%) overestimated and 3 (2%) underestimated their daily PA by more than one day. Intraclass correlation (ICC) revealed a poor association of self-reported and objectively measured PA in ACHD (r=.231, p<.038) and a moderate association (r=.503, p<.001) in RC. Detailed overview on the agreement is given in Figure 20

Figure 20: Agreement of subjective vs. objective assessment of physical activity in 184 ACHD and 119 healthy controls



Discussion

In this cross-sectional study, we found both ACHD and healthy controls not to be sufficiently physically active against international guidelines of the WHO [35] regarding their MVPA. Furthermore, MVPA was even lower in ACHD than RC. In terms of daily steps both groups accumulated a relatively high amount and can be considered quite active.

Although there is currently no scientific recommendation on daily steps, 10.000 steps/ day is widely considered a reasonable goal [71]. Regarding the lack of sufficient PA in the general population worldwide independent of age, sex, income [103] our findings in ACHD are alarming, but not surprising.

While both ACHD and healthy controls are quite active considering their daily steps, it becomes apparent that generally they seem to lack intensity in their PA behavior. Patients with CHD have been encouraged to live an active lifestyle for a couple of decades now but at the same time still were advised to be cautious when it comes to intense PA and sports [185]. A relatively high amount of daily steps (Table 16) points to the idea that our cohort generally does seek active leisure time activities but at the same time does lack intensity in their PA. One explanation could be that older generations in our cohort were potentially advised to be conservative when it comes more intense activities and sports- even though a certain high level of intensity in PA is imperative for cardiovascular benefits [10].

Previous studies on children with CHD have shown them to generally be quite active, and accurate in estimating their activity levels [123], while our results suggest the picture to be different in adult patients. In fact, 75% of a German cohort of children with CHD reached the recommended activity levels on a daily basis [123], and only 17% of our German ACHD did so. Considerations about why ACHD are not physically active enough are multifactorial. ACHD have a reduced physical capacity [129,189] and might therefore not be capable to be as active as otherwise healthy. This can result in a vicious cycle leading to even less physical activity and again more reduced physical capacity. Additionally, overprotective advice - self-induced or through medical professionals [97,190] - can have patients refrain from a physically active lifestyle [95,191]. While otherwise healthy already struggle with getting enough PA, ACHD possibly need to overcome additional hurdles. We know that PA behavior generally tracks well into adulthood [38]. Therefore, at this point clinicians can hopefully trust that a more active generation of young patients with CHD is growing up. However, in the meantime we cannot forget about the current adult patients who are clearly not active enough. PA interventions can provide a safe approach[182].

Similarly, we found moderate, complex and surgically corrected CHD to be even less active than our healthy reference cohort. Complex CHD are - by definition of the word - more complicated than simple. Patients with higher severity class might therefore feel more limited by their chronic disease than patients with simple defects or otherwise

healthy, thus resulting to less active and especially intense movement. Generally, patients with a more complex CHD are at a higher risk for decreased exercise capacity, hospitalization or death [102]. Therefore, complex CHD specifically could benefit from encouragement towards more PA. Especially considering that PA is known to be reduced in patients with lower VO_2peak [125] - an important predictor for mortality in CHD [102]. Considering that the small sample size in simple ACHD led to this group not reaching statistical significance in our analysis, the encouragement towards more PA can most likely be extended to all ACHD regardless of severity class.

Subjective vs. objective PA

Our results are partly in contrast with the most recent study on the topic which found ACHD to be similarly active as a healthy reference [128]. However, in line with Larsson et al. [128] we confirmed that ACHD even more extensively than healthy subjects fail to estimate their weekly activity but tend to overestimate how active they really are. Considering this contrast in subjective estimation and objective reality, it is no surprise that ACHD are not active enough. If ACHD were as active as they pretended they would achieve the WHO recommendation of 150 MVPA per week. In their subjective assessment they are not aware of the incorrectness of their estimation, and hence do not see the need to change their behavior. Thus, in clinical routine it might be suitable to objectively evaluate PA and thereby alert ACHD with insufficient PA behavior. This is similar to exercise capacity, that is also overestimated by adolescents and adults with CHD in questionnaires [180]. While it is speculative why patients and healthy overestimate themselves, it is imperative for medical professionals to be aware if this tendency. Objective PA measurement could provide a complementary examination for patients at risk of not getting enough PA, while trustful reliance on correct self-estimation cannot be given based on our findings.

Limitations

The inbuilt algorithm of the wearable used that records MVPA only if bouts of at least 10 minutes are reached, might be in line with current WHO recommendations for PA while the data was collected [35]. However, after a recent update the WHO PA guidelines now doe not consider these 10-minute bouts anymore [26]. In light of this softer criterion MVPA minutes are much more difficult to achieve if only recorded for 10 minutes continuously instead of counting every minute. This could possibly lead to an underrepresentation of measured MVPA in our study and to comparison bias to other studies. Also, the wearable used in our study does not differentiate between moderate and vigorous physical activity

and according to the WHO, the latter should count double. This also affected the total MVPA. As study participation was voluntary, a self-selection bias towards more active participants needs to be considered. Furthermore, the well documented Hawthorne effect by which individuals might alter their behavior in response to their awareness of being observed [74] could also influence our results. While we managed to achieve a relatively high sample size, the number of patients with simple CHD is still relatively low. Larger sample sizes could further validate our findings.

Conclusion

While ACHD moved around quite a bit considering their relatively high number of steps, they lacked intensity in their PA behavior, were less active than healthy controls, and failed to reach the WHO recommendation on PA. If not restricted by rare findings that make vigorous activity dangerous [192] they need encouragement towards more intense movement to improve exercise capacity and lower cardiovascular risk. Self-reported PA showed no agreement to the objectively measured PA.

3.8 Discussion of Publication IV

The findings of the last publication on adult patients are at first sight completely contrary to the previous two publications on children with CHD. ACHD do not move intense enough. However, considering these findings in the light of adolescents with CHD also having a higher likelihood of not being active enough in publication II, they fall in line with what is known about PA in general. A physically active lifestyle decreases with increasing age [2]. Physicians and other clinical professionals started with increasingly encouraging patients with CHD to be active about two decades ago. Maybe this timeframe was not sufficient enough to alter previously engraved hesitant behavior when it comes to exercise and PA. Especially older patients might still be overly careful when it comes to moving intensely. Educating this patient group on the benefits of regular PA could be one solution [96,98].

At this point, the update to the WHO Guidelines on PA and sedentary behavior from November 2020 is important to consider again [26]. During the data collection for the publication IV of this dissertation, the WHO recommendation asked for bouts of at least 10 minutes continuous MVPA [35]. However, with this recent update, these 10-minute bouts are now obsolete, and every MVPA minutes now counts for adults as well. However, the measurement device employed in this publication (Garmin vivofit 3) has an inbuilt algorithm which adheres to 10-minute bout criterion. While this does not change the main findings, it is important to be kept in mind.

A further crucial endeavor is therefore keeping patients active over the transition period into adulthood. As mentioned previously, PA in childhood is about establishing good and healthy habits, while PA in adulthood is focused on the prevention of secondary diseases. Based on the findings of the publication IV of this dissertation, there seems to be further potential for improvement in adult patients with CHD. This is especially crucial with increasingly secondary diseases in older patients with CHD, and a generally aging CHD population [9].

4 Summary

The main focus point of this dissertation was on objectively assessed PA in patients with congenital heart disease, especially on wearable tracking devices as a measurement tool. The findings of this dissertation are manifold.

A systematic literature review found that the overall study quality of research on the topic was fair at best and that the included studies lack comparability due to methodological differences. Therefore, based on previous research on objective physical activity assessment, no conclusive answer on how active patients with CHD really are, can currently be given.

In three cross-sectional studies with wearable PA tracking devices on a self-recruited cohort of young children, adolescents, and adults with CHD, it was found that the majority of children and adolescents with CHD are sufficiently active. However, PA needs to be promoted in young patients who are overweight, obese, or of complex CHD severity. Furthermore, the more active young patients with CHD are, the higher their likelihood to be happier in the form of better HRQoL. Adult patients with CHD on the other hand lacked intensity in their daily movement and need to be encouraged to move more as they are failing to reach general PA recommendations as well as PA levels of their healthy peers. This is especially crucial in the context of lower exercise capacity in this cohort and an aging CHD population possibly at risk for cardiovascular diseases [11].

And lastly, subjective PA estimation of young patients is fairly correct in about half of all children with CHD while the large majority of adult patients overestimate how active they really are. In other words, the older the patients with CHD, the less active they are and the less accurate their subjective estimation of their PA behavior.

5 Clinical Perspective and Future Research

The fact that a physically active lifestyle declines with increasing age in the CHD cohorts included in the publications of this dissertation is not surprising, as this depicts the trend of the general population [35]. Aside from age, sex, and motivation, the individually perceived health-status are crucial individual correlates of PA. On a broader, more general level, the social and physical environment also contribute to an active lifestyle [193]. More importantly, the age-related decline of PA can increasingly be attributed to the switch to inaction during leisure time activity at home and occupational sedentary behavior as people developed from active children into inactive adults. Together with increasingly passive modes of transportation with increasing age, it is no surprise that our CHD cohort shows similar activity patterns with increasing age as the general population [35]. Furthermore, even though they are chronically ill, patients with CHD are well-integrated into the normal life [7]. Therefore, the adult CHD population showing similar activity patterns as the general population is not surprising.

Nevertheless, the pressing issue is the question of how these patients, who are clearly not active enough, can effectively be encouraged to be more active? The majority of all patients with CHD can and should reach general population recommendations on PA as it is considered safe and beneficial with limitations in only very few individual cases [10,99]. Understanding why people are physically inactive or active helps to answer this question, and ultimately helps to reduce future effects of the current and worldwide physical inactivity pandemic and further prevent non-communicable diseases [193].

Interventions to increase PA are a relatively new field of research, and currently there is not enough evidence to conclusively determine the impact of physical activity interventions in patients with CHD [182]. However, the number of adverse events in all PA intervention studies on patients with CHD was negligible implying that such interventions are safe even in a home-based setting [194]. The search must continue to find the right dose-response relationship to effectively increase PA especially in adult patients with CHD. The line between initiating a training effect and not endangering patients with CHD is thin but must be explored in more detail as adult patients with CHD are clearly not active enough.

Adult patients with CHD who are currently not tied to specialized healthcare structures represent another perspective that needs to be considered in the context of the findings of this dissertation. The cohort of the studies of this dissertation was recruited at the

German Heart Center Munich, one of the most specialized centers for patients with CHD. However, the medical staff there only sees a small proportion of all patients currently living with CHD in Germany. In fact, specialized CHD centers are still underutilized in Germany even though general practitioners are not adequately informed and there is great need for specialist guidance [195]. Patients with CHD who are currently not in regular follow-up at specialized centers cannot be forgotten about. Better awareness, optimized care and improved patient-caregiver relationships are still needed for a lifelong and holistic medical care approach of patients with CHD [196], including the encouragement towards more PA.

While this dissertation supplies some mosaic pieces to the greater picture of a holistic approach medical aftercare in patients with CHD, it also raises some insights into further research perspectives.

The cohort of patients with CHD at the German Heart Center Munich in the FOOT-LOOSE (DRKS-ID: DRKS00018853) and CARING (DRKS-ID: DRKS00015248) project is quite large and diverse, with tremendous possible insights into PA, arterial stiffness, motor skills, or physical capacity. In light of the findings of this dissertation a next possible step could be further looking into the relationship between PA and arterial stiffness across the ages in patients with CHD.

Furthermore, adult patients with CHD lack sufficient PA levels. Why exactly this is be the case must be further explored. Therefore, an interesting area for research would be exploring the triangular relationship between everyday PA (measured with wearable tracking devices), exercise capacity (measured with cardiopulmonary exercise testing), and heart-focused anxiety (measured with the Cardiac Anxiety Questionnaire [197]). Due to many doctoral visits and the awareness of the congenital disease that accompanies these patients since birth, they might not only be more sensitive, but might also pay more attention to their heart. Determining whether it is fear of cardiac-related stimuli and sensations because of their perceived negative consequences that inhibits adult patients with CHD to be more active is imperative as medical aftercare is pursuing a holistic approach to health.

Additionally, the field of PA in patients with CHD needs to gain further understanding of subgroups at risk of not being active enough. While ongoing studies such as the FOOT-LOOSE and the CARING project at the German Heart Center Munich will gather this understanding in the upcoming years, considerations need to already be made how patients who are not active enough can be effectively supported in being more active. One

major focal point should thereby be regular and continuous education and encouragement. A lack of knowledge, experience and awareness of one's own capacity and everyday activity paired with reduced physical capacity can increase the tendency to be less active, which in turn worsens physical capacity. This addresses two important concerns: how can active children be kept active into adulthood, and how can inactive adult patients become more active.

More than that, it will be important to consider what can be learned about PA behavior from the children of the included cohort of this dissertation. They are quite active and interesting to be further evaluated for take-aways for other chronically ill and also healthy populations. While the world is struggling with 80% of its children and adolescents not being active enough [28], we are following a cohort where 80% of the children are very active. Why might that be the case? Is it due to very regular information with reoccurring doctoral visits every year? Or maybe their high awareness of disease status and that health needs to be actively sustained? If in future research it can further determined what makes these children so active, we might be gaining a further piece of the puzzle in the worldwide quest of being more physically active.

Finishing on some conclusive yet less scientific thoughts, the value of sports- and health-science related studies in outpatient clinics for chronically ill should not be underestimated. The presence of sports scientists, who have been involved in various studies in the outpatient setting of the German Heart Center Munich for a good decade now, certainly might contribute to the fact that we observe and accompany quite active children with CHD. Many of these children have been included in our studies several times, and almost every regular doctor's appointment reminds them in some way that exercise and physical activity are an integral part of a healthy and long life. The presence and work of sports- and health scientists creates synergies all parties involved – patients, parents, primary caregivers, medical staff, and other stakeholders – can benefit from. Ultimately the sum of such synergies is greater than its individual parts and helps to achieve a more holistic approach to patient care.

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