Cardiovascular Risk in Patients with Congenital Heart Disease

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Cardiovascular risk in patients with congenital heart disease

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Summary

Congenital heart diseases are counted among the most frequent congenital diseases. Over the last decades, life expectancy increased in these patients and 90% of the children with congenital heart disease reach adulthood. Thus, age-related cardiovascular diseases become a relevant risk for patients with congenital heart disease as cardiovascular diseases are the main cause of death in the aging population throughout the world.

In this PhD thesis, certain risk factors for cardiovascular diseases were analyzed in order to quantify the risk of age-related cardiovascular diseases in patients with congenital heart disease. Analysis revealed that arterial stiffness is increased in children with congenital heart disease compared to healthy peers, and adults with congenital heart disease with Metabolic syndrome are affected by a higher carotid intima-media thickness than adults with congenital heart disease without Metabolic syndrome. Therefore, these two analyses showed increased cardiovascular risk factors. However, according to the PROCAM risk score, adults with congenital heart disease have a lower 10-year risk for major cardiovascular events compared to a healthy reference population.

Based on these three analyses, the research question of this work cannot be answered clearly as their results are heterogeneous, showing different risk potentials for age-related cardiovascular diseases.

In conclusion, despite the heterogeneous results, the single risk factors for cardiovascular diseases have to be kept at a minimum and regularly controlled in individuals with congenital heart disease in order to limit the risk of cardiovascular events and diseases. Since adults with congenital heart disease usually died in younger ages in the past, the analysed risk factors were not relevant so far due to low exposure time. But future studies have to further evaluate the single components in terms of their effect on mortality and morbidity for individuals with congenital heart disease.

Zusammenfassung

Angeborene Herzerkrankungen zählen zu den häufigsten angeborenen Anomalien. In den letzten Jahrzehnten ist die Lebenserwartung dieser Patienten gestiegen und 90% der Kinder mit angeborenem Herzfehler erreichen das Erwachsenenalter. Da Herz-Kreislauf-Erkrankungen weltweit die Haupttodesursache in der alternden Bevölkerung sind, werden somit altersbedingte Herz-Kreislauf-Erkrankungen zu einem relevanten Risiko für Patienten mit angeborenem Herzfehlern.

In dieser Doktorarbeit wurden bestimmte Risikofaktoren für Herz-Kreislauf-Erkrankungen analysiert, um das Risiko altersbedingter Herz-Kreislauf-Erkrankungen bei Patienten mit angeborenem Herzfehler zu quantifizieren. Die Analyse ergab, dass die arterielle Steifigkeit bei Kindern mit angeborenem Herzfehler im Vergleich zu gesunden Gleichaltrigen erhöht ist und dass Erwachsene mit angeborenem Herzfehler und dem Metabolischen Syndrom von einer dickeren carotiden Intima-Media-Dicke betroffen sind als Erwachsene mit angeborenem Herzfehler ohne das Metabolischen Syndrom. Daher zeigten diese beiden Analysen erhöhte kardiovaskuläre Risikofaktoren. Laut dem PROCAM-Risiko-Score haben Erwachsene mit angeborenem Herzfehler jedoch im Vergleich zu einer gesunden Referenzpopulation ein geringeres 10-Jahres-Risiko für ein großes kardiovaskuläres Ereignis.

Auf der Grundlage dieser drei Analysen kann die Forschungsfrage dieser Arbeit nicht eindeutig beantwortet werden, da die Ergebnisse heterogen sind und unterschiedliche Risikopotenziale für altersbedingte kardiovaskuläre Erkrankungen aufzeigen.

Zusammenfassend lässt sich sagen, dass trotz der heterogenen Ergebnisse die einzelnen Risikofaktoren für kardiovaskuläre Erkrankungen bei Patienten mit angeborenem Herzfehler auf einem Minimum gehalten und regelmäßig kontrolliert werden müssen, um das Risiko für kardiovaskuläre Ereignisse und Erkrankungen zu begrenzen. Da die Erwachsenen mit angeborenem Herzfehler in der

Vergangenheit meist in jüngeren Jahren verstarben, waren die analysierten Risikofaktoren aufgrund der geringen Expositionszeit bisher nicht relevant. Zukünftige Studien müssen jedoch die einzelnen Komponenten hinsichtlich ihrer Wirkung auf Mortalität und Morbidität bei Patienten mit angeborenem Herzfehler weiterevaluieren.

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List of Abbreviations

ACHD	Adults with Congenital Heart Disease
AS	Valvular Aortic Stenosis
ASD	Artrial Septal Defect
AVSD	Atrioventricular Septal Defect
CHD	Congenital Heart Disease
cIMT	Carotid Intima-Media Thickness
CoA	Coarctation of the Aorta
EBS	Ebstein's Anomaly
$HbA1_c$	Haemoglobin $A1_c$
HDL	High-density lipoprotein cholesterol
HLHS	Hypoplastic Left Heart Syndrome
LDL	Low-density lipoprotein cholesterol
MetS	Metabolic Syndrome
PAN	Prävalenz angeborener Herzfehler bei Neugeborenen in Deutschland (Prevalence of congenital heart disease in newborns in Germany)
PDA	Patent Ductus Arteriosus
PFO	Patent Foramen Ovale
PS	Pulmonary Stenosis
TAC	Truncus Arteriosus Communis
TAPVC	Total Anomalous Pulmonary Venous Connection
TCPC	Total Cavopulmonary Connection
TGA	Transposition of the Great Arteries
ToF	Tetralogy of Fallot
UVH	Univentricular Heart
VSD	Ventricular Septal Defect

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1 General introduction

As soon as in the fourth week of pregnancy, the heart of an embryo starts beating. The heart consists of two parts with atriums, ventricles and emission sections by the sixth week.[1] In this crucial phase of embryonic development, certain malformations can occur, resulting in congenital heart diseases (CHD).[2] With an incidence of 1 to 100 of all live births worldwide,[3] CHD are counted among the most frequent congenital disease which was, for a long time, considered incurable and not compatible with life.[4]

On the pursuit of correctional interventions, it has been an outstanding challenge to open the heart while maintaining the brain circulation.[5] In 1952, the first breakthrough was achieved, when Floyd John Lewis corrected an atrial septal defect (ASD) in just over five minutes at the University of Minnesota. By cooling a 5-year-old girl with the ASD to 27°C, oxygen consumption was minimized, enabling cardiac arrest. This was the first corrective intervention at an open heart. The second breakthrough – maintaining brain circulation – was done in 1953 by John Gibbon at Mayo Clinic. He first developed and applied the heart-lung-by-pass machine to close an ASD in an 18-year-old woman.[5]

As a result of these, and other improved surgical techniques, prenatal diagnoses of the CHD, and enhanced aftercare treatments, mortality rate tremendously decreased and life expectancy increased in individuals with CHD over the last decades (cf. Figure 1).[6-9]

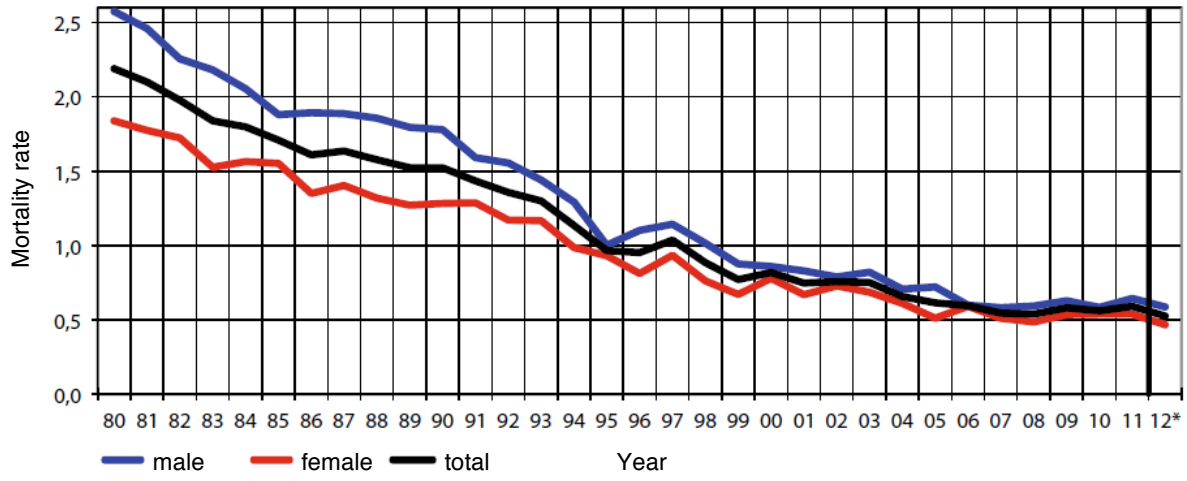


Figure 1: Development of the mortality rate of congenital malformation (ICD-10 Q20–Q28) by sex in Germany from 1980 to 2012 (translated from Aumiller and colleagues[3])

As a result, 90% of the children with CHD live beyond the age of 18.[10, 11] Therefore, it is not surprising that in the United States, it has been more than a decade that there are more adults with CHD (ACHD) than children with CHD.[12] Also data from Quebec, Canada, showed that two thirds of all patients with CHD are ACHD.[13] In Germany, the proportion of ACHD is also rising and estimated to be around 180,000 – 280,000.[14]

This redistribution in the patients' structure reflects the paradigm shift from perioperative to chronic mortality.[6-8] Even though corrective surgery has high success rates, patients with CHD are rarely cured and late complications are common. Apart from the underlying congenital heart defect, consequences of surgery and medical treatment can also result in late morbidity, as many suffer from postoperative residua and sequelae.[15] Complications may also include pulmonary hypertension, thromboembolism, and heart failure.[16]

So far it is not clear how individuals with CHD are affected by age-related diseases as compared to the normal population. As many of the alterations and complications of the individuals with CHD are related to the cardiovascular system, and with an increasing life expectancy in this group, it is not clear yet how the aging process affects the risk of cardiovascular diseases in higher ages among ACHD.

2 Cardiovascular diseases and risks

Cardiovascular diseases are the main cause of death in the aging population throughout the world. Eighty percent of all deaths related to cardiovascular diseases are induced by heart attacks and strokes.[7] However, the majority of cardiovascular diseases are preventable according to the World Health Organization.[17]

Cardiovascular diseases are induced by certain risk factors such as hypertension, arterial stiffness, Metabolic Syndrome (MetS), dyslipidemia, overweight and obesity, smoking, diabetes mellitus, and family predisposition.[18-25]

Elevated blood pressure was found in ACHD, and in patients with a repaired coarctation of the aorta (CoA) hypertension is the main complication and associated with increased Body Mass Index, the male sex, and increasing age.[26, 27]

A further risk factor for cardiovascular diseases is the central blood pressure (aortal pressure) as it is a surrogate measure of arterial stiffness and therefore a characteristic for the vascular function.[28] Increased arterial stiffness and a stiffer vasculature was found in children with CHD.[29-33] Children with CHD after arterial switch operation and children with intrinsic coronary abnormalities are also at an increased risk for early atherosclerosis.[34] In addition, in the general population, atherosclerotic alterations begin in childhood [35] and it is known that cardiovascular risk factors persist from childhood to adulthood.[35, 36]

Another risk factor for cardiovascular disease is the MetS [23, 24] which is also associated with a higher cardiovascular mortality and all-cause mortality and morbidity.[24, 37-39] It is a frequent metabolic disorder and a crucial public-health challenge [40] and depending on the definition criteria, 10-40% suffer from MetS worldwide.[41] Some studies indicate that the prevalence of MetS is more frequent in ACHD compared to healthy controls.[42, 43]

Various risk factors define the syndrome, which include increased serum triglycerides, raised blood pressure, decreased high-density lipoprotein, high fasting

plasma glucose, visceral or central obesity, and high haemoglobin $A1_c$ ($HbA1_c$). Underlying risks are unhealthy diet with high amounts of saturated fat, simple sugar and cholesterol, physical inactivity, higher age, and hormonal imbalance.[23] Some consequences are triggered by increased pro-inflammatory markers and activated sympathetic nervous and renin-angiotensin systems. This activation leads to pathophysiologic changes like atherosclerosis and vascular calcification in the arteries.[44]

The relation between MetS and atherosclerosis is also demonstrated with the Metabolic Syndrome Severity Calculator showing “a good predictive power to detect carotid plaque”.[45] Carotid plaques are pathophysiological changes at the arteria carotis communis and the severity of pathophysiological changes is indicated by the carotid Intima-Media Thickness (cIMT).[46] A recently published study demonstrated in 4724 participants that maximum cIMT added significantly to the predictive power of incident cardiovascular disease.[47] Therefore, the cIMT is a surrogate end point of cardiovascular outcomes and a risk factor for cardiovascular diseases.[46] First study results indicated an increased cIMT in children with CHD compared with a healthy reference. Children with CoA and transposition of the great arteries (TGA) after arterial switch had the highest cIMT values.[48]

Apart from the single analysis of the risk factors and their effects on cardiovascular diseases, a holistic approach describes the actual cardiovascular risk in a better way. Various scores exist to calculate the risk based on different anthropometric data, blood values, smoking status and family predisposition. The most widely known are the PROCAM (Prospective Cardiovascular Münster) Study,[49] Framingham Study,[50] and Reynolds risk score.[51, 52]

Several studies also demonstrated that the underlying risk factors of the scores are abnormal in ACHD.[22, 42, 43, 53-57] Obesity occurs more frequently in patients with CHD than in the general population.[22, 43] Furthermore, decreased high-density lipoprotein (HDL) cholesterol as well as elevated low-density lipoprotein

(LDL) cholesterol and triglycerides were found in ACHD.[43, 53, 58] Increased incidence of diabetes type 2 was also found in ACHD.[54]

3 Study purpose

Considering the fact that patients with CHD grow older and as single risk factors of cardiovascular diseases become more relevant for these patients, cardiovascular diseases are suspected to be an increasing problem in this population. In addition, many of the complications and medical consequences for the individuals with CHD are related to the cardiovascular system.

Therefore, the purpose of this study is to quantify the actual age-related cardiovascular risk in patients with CHD compared to the general population.

4 Medical background

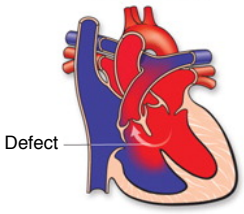
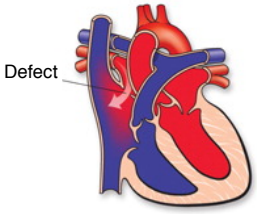
4.1 Overview of Congenital Heart Diseases

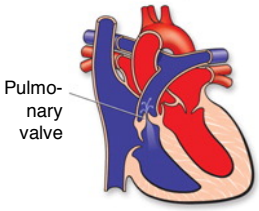
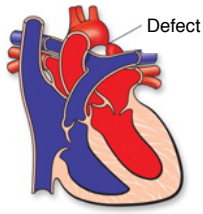
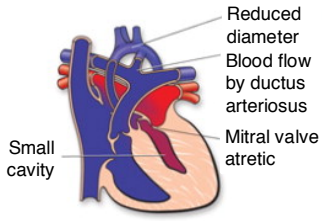
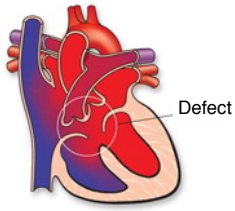
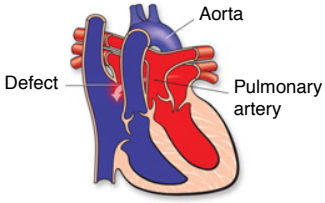
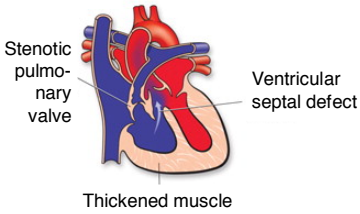
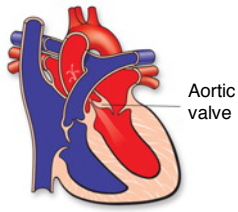
CHDs are structural anomalies of the heart and/or of the great thoracic vessels with actual and potential impairments of functionality.[59]

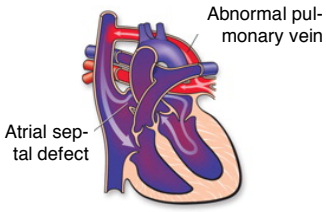
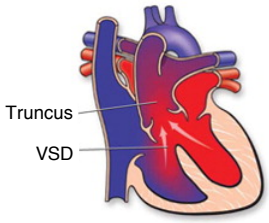
According to the definition of Connelly and colleagues,[60] the anomalies can be defined as simple, moderate or severe CHD depending on the complexity of the guiding anomaly. A further classification can be made according to the type and the localization of the impairment into five major subgroups: “left heart obstruction” including aortic stenosis and CoA, “right heart obstruction” including Tetralogy of Fallot and Pulmonic Stenosis, “isolated shunts” including atrial/ventricular/atrioventricular septal defect, “TGA after arterial switch” and children after ”total-pulmonary connection”.

An overview with a short description of the most common CHDs is given in Table 1. The prevalence relates to 10,000 live births in Germany and was determined in the PAN (Prävalenz angeborener Herzfehler bei Neugeborenen in Deutschland / Prevalence of congenital heart disease in newborns in Germany).[61]

Table 1: Overview of congenital heart diseases [10, 62]

CHD	Prevalence[a]	Description	Impression
VSD	52.7	The septum between the ventricles has a hole which allows oxygen-rich blood to leak into the oxygen-poor blood ventricle. Trapped blood causes higher pressure inside the heart, potentially inducing lower oxygen saturation.	
ASD	18.3	The septum between the atria has a hole which allows oxygen-rich blood to leak into oxygen-poor blood in the right atrium. A lower oxygen saturation may be induced.	

CHD	Prevalence[a]	Description	Impression
PS	6.6	A thickened arteria pulmonalis or a deformed valva trunci pulmonalis results in a narrowed ventriculus sinister outlet and hampers normal blood flow to the lungs. Backlog of the blood induces a hypertrophy of the right ventricle.	
CoA	3.9	The aorta has a stenosis in the area of the ligamentum arteriosum insertion which affects the blood flow. A higher blood pressure and a left ventricular hypotrophy may be a consequence.	
UVH	3.0	Functioning of only one ventricle. Common is the HLHS (underdevelopment of the aorta, valva aortae, ventriculus sinister and valva atrioventricularis sinistra). *Oxygenated and oxygenpoor blood mixes by PFO and AS leading to lower oxygen saturation.*	
AVSD	2.7	Combination of ASD and VSD. Oxygen-rich blood from the lungs mixes with oxygen-poor blood from the body and the blood is not routed properly to each station of circulation.	
TGA	2.7	Reversion of aorta and pulmonary artery so that two separate circulations exist and no oxygen-rich blood circulates in the body. Survival is possible only by a PFO, PDA, ASD or VSD.	
ToF	2.7	Combination of four defects: VSD, PS, overriding aorta situated above the VSD, hypertrophy of the right ventricle.	
AS	2.4	The aortic valve does not open and close properly resulting in a narrowed ventriculus sinister outlet and leaking blood. Trapped blood may build pressure inside the heart and cause left ventricular hypotrophy.	

CHD	Prevalence[a]	Description	Impression
TAPVC	0.6	The pulmonary veins are malpositioned and lead to the right atrium, frequently in combination with a VSD. Survival is possible only by a PFO or ASD. Oxygen-rich blood mixes with oxygen-poor blood leading to lower oxygen saturation.	
TAC	0.5	One arterial trunk arises from the heart, very often in combination with a VSD. Oxygen-rich blood mixes with oxygen-poor blood, leading to lower oxygen saturation.	
EBS	0.4	The tricuspid valve is deformed and displaced downwards in the right ventricle leading to tricuspid regurgitation and right heart failure.	

ASD: Atrial Septal Defect, AS: Valvular Aortic Stenosis, AVSD: Atrioventricular Septal Defect, CHD: Congenital Heart Disease, CoA: Coarctation of Aorta, EBS: Ebstein's Anomaly, HLHS: Hypoplastic Left Heart Syndrome, PDA: Patent Ductus Arteriosus, PFO: Patent Foramen Ovale, PS: Pulmonary Stenosis, TAC: Truncus Arteriosus Communis, TAPVC: Total Anomalous Pulmonary Venous Connection, TGA: Transposition of the Great Arteries, ToF: Tetralogy of Fallot, UVH: Univentricular Heart, VSD: Ventricular Septal Defect

[a]: Prevalence per 10,000 live births in Germany [61]

Uncorrectable or inadequately corrected CHD may cause central cyanosis. Cyanosis is a symptomatic description where the skin and mucous membranes appear in a blue coloration.[63] A central cyanosis exists if hemoglobin, a ferrous protein in the erythrocytes, is not sufficiently oxygenated, as oxygenated and not-oxygenate blood mixes due to the underlying CHD. This leads to a lower oxygen supply.[63] Measured by pulse oximetry, a cyanosis is mostly apparent in an oxygen saturation lower than 85%, sometimes even when the oxygen saturation is lower than 75% (standard value: 95-99%).[64, 65]

4.2 Blood biomarkers

4.2.1 High-density lipoprotein cholesterol (HDL)

HDL cholesterol is a plasma lipoprotein with the highest density. Most of the HDL cholesterols are spherical and have a fatty core with a covering of phospholipids, free cholesterol, and apolipoproteins. They can be divided into several subgroups according to their shape, size, density, apolipoprotein composition, and surface charge.[66]

HDL cholesterol is produced as discoidal lipid-poor particle in the liver and intestine. It acquires most of its lipid components in the plasma. The function of HDL cholesterol is classified into the transportation of plasma cholesterol and the non-lipid functions with the potential to protect against cardiovascular diseases. These protective functions include the following properties: antioxidant, anti-inflammatory, antithrombotic, enhancing the endothelial function, and endothelial repair.[66]

According to European Guidelines, for men a low HDL cholesterol was defined at <40 mg/dl and for women at <45 mg/dl.[67] However, HDL cholesterol values that are too low are independently associated with an increased cardiovascular risk.[67, 68]

4.2.2 Low-density lipoprotein cholesterol (LDL)

LDL cholesterols have a lower density than HDL cholesterol but they are very similar in shape and form, as they also have a hydrophobic core surrounded by phospholipids and free cholesterol.[69] However, a single apolipoprotein (apoB100) encases almost 30% of the LDL cholesterols and therefore is an important factor concerning the lipid metabolism and the atherosclerosis' pathophysiology.[70]

Even though the apoB100 also exists in the very-low-density lipoprotein and intermediate-density lipoprotein, LDL cholesterols have the highest association with elevated cardiovascular risk.[69] In an epidemiological and clinical trial,

Grundy and colleagues reported a log-linear link between LDL cholesterols and the relative risk for cardiovascular diseases, meaning with each 30-mg/dl decrease in LDL cholesterols a relative reduction in risk for coronary heart disease of almost 30% (cf. Figure 2).[71]

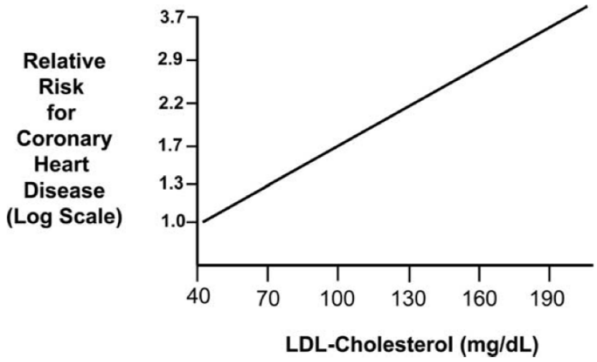


Figure 2: Log-linear link between LDL cholesterols and the relative risk for cardiovascular diseases
LDL: low-density lipoprotein

Furthermore, according to European Guidelines [68] a LDL cholesterol value of 190 mg/dl should not be exceeded, as long as no further cardiovascular risk factors are present. If other risk factors are present, lipid lowering has to be started with lower LDL cholesterols values.[68]

4.2.3 Triglycerides

In lipogenesis in fatty tissue, but also in other cells, triglycerides are ester bound between the alcohol, glycerin and three fatty acids of different chain length and degree of saturation.[72, 73]

The fatty acids come from food or they are made by the body itself.[72] Triglycerides are the most common lipids in humans and serve as storage material for times of need.[68, 73] However, if the proportion of triglycerides in the blood is increased (>150 mg/dl) it indicates an elevated risk of cardiovascular disease. Furthermore, low HDL cholesterol values and high amounts of small dense LDL cholesterols are often associated with high triglyceride levels.[68]

4.2.4 Glycated Hemoglobin

Hemoglobin transports oxygen and carbon dioxide in the body. If glucose is absorbed by the erythrocytes and is not completely metabolized, but is partially and irreversibly bounded to hemoglobin, it is leading to glycated hemoglobin ($HbA1_c$). Since glycated hemoglobin is present in the erythrocytes until their degradation, the $HbA1_c$ value retrospectively reports the blood sugar concentration level during the last 4 to 6 weeks. Thereby, in diabetes patients the therapy of the last 4 to 6 weeks can be objectively controlled. A healthy $HbA1_c$ level is between 4% to 6%, but in patients with diabetes mellitus this level can rise up to 12%.[74]

The American Diabetes Association[75] recommends the use of the $HbA1_c$ test for the diagnosis of diabetes mellitus and a value ranging from 5.7% to 6.4% of $HbA1_c$ defines individuals at a high risk of diabetes. Additionally, according to European Guidelines, a $HbA1_c$ value higher than 6.5% was defined as diabetes mellitus type 2.[67, 68]

5 Methodology

5.1 Study design

This PhD thesis is a confirmatory study. The sample size estimation was planned for the adult patients with CHD, the measurement results of the children with CHD exist from an earlier work.

The sample size calculation was performed based on the outcome of the PROCAM score with a mean age of 40-45 years in the study population. According to the PROCAM score (cf. *5.6 Cardiovascular risk score*), the average risk of a major cardiovascular event within the next 10 years for this age group is around 2%.[76] Considering the assumption that this risk is 10% higher in ACHD, which yields a total percentage of 2.2%, results in the following calculation with a minimum of 302 study patients:

Table 2: Sample size estimation for ACHD

Incidence healthy population	2.0 %
Standard deviation	1.0
Incidence ACHD	2.2 %
Standard deviation	1.1
Alpha	0.05
Power	0.95
Effect size	0.19
Sample size	**302**
Actual power	**0.95**

ACHD: Adults with congenital heart disease

5.2 Study participants

The investigation was performed at the German Heart Centre in Munich, a specialized center for cardiovascular diseases and state of the art medical treatment. It was founded between 1972 and 1973.

In 2017, 20.000 patients were treated at the center on an outpatient basis. Out of these patients, 6.480 visited the Department of Pediatric Cardiology and Congenital Heart Defects.

Among the patients visiting the department of Pediatric Cardiology and Congenital Heart Defects for a routine follow-up, test persons between six and 18 years or older than 30 years (in line with the Framingham Study[77]) were recruited.

In total, 648 ACHD (43.9 ± 10.2 years, 47.7% female) with various CHDs were prospectively examined between February 2017 and November 2018. Since there have been few investigations with children with CHD in recent years, there were 988 children with CHD (39.5% girls, 12.5 ± 3.5 years) tested by different examiners between July 2014 and February 2017. The following *Figure 2* demonstrates the measurements performed in children and adults with CHD and the respective examination numbers.

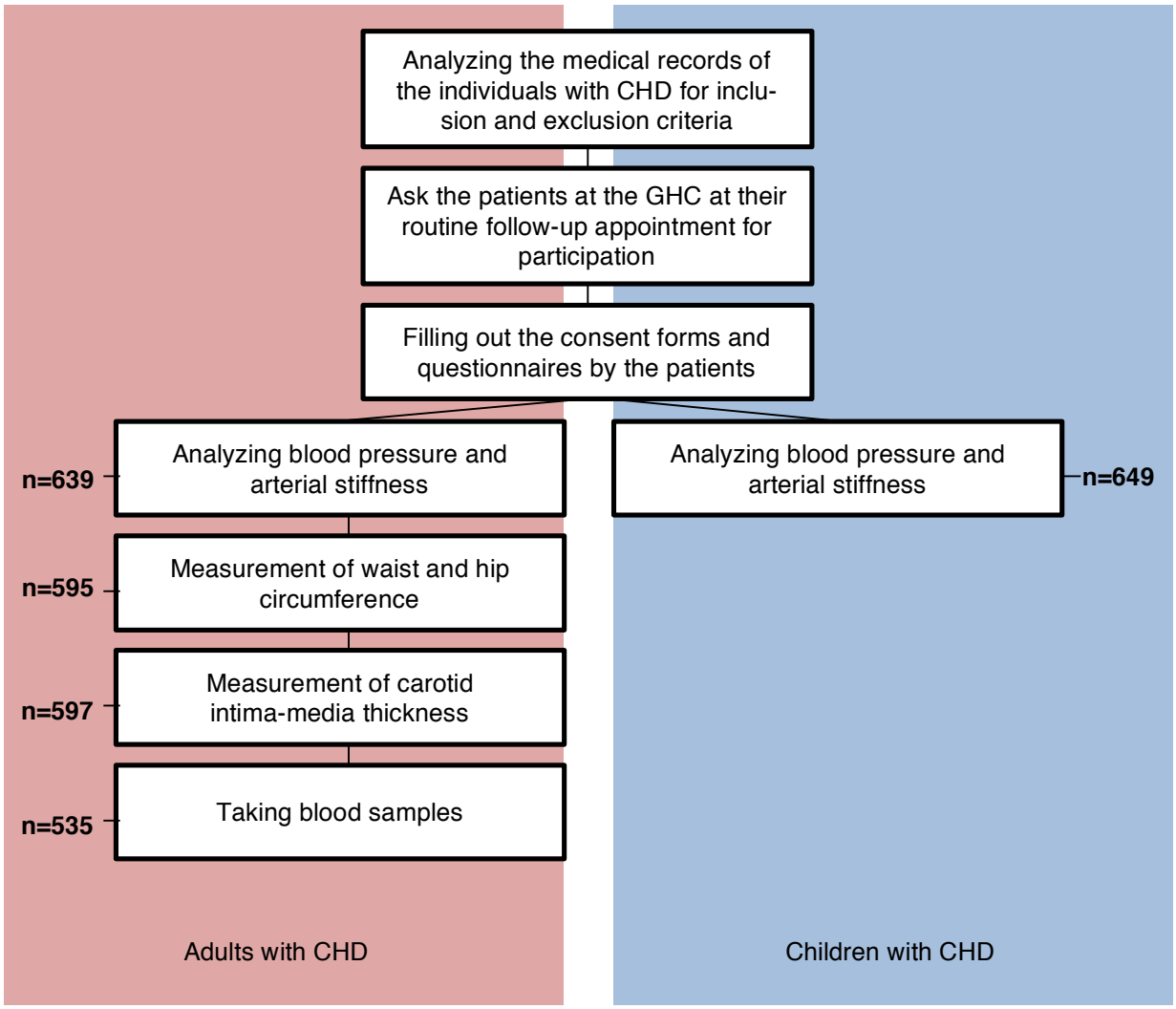


Figure 2: Overview of the measurements and the number of examinations

CHD: Congenital heart disease; GHC: German Heart Center

The consent form of the children is available in *Appendix A* and *B,* and for the adults in *Appendix C*.

5.3 Research methods

5.3.1 Blood pressure and arterial stiffness

In all patients, the blood pressure was measured with the Mobil-o-Graph device of I.E.M, a German company (cf. Figure 2). The patient has been lying in supine position for five minutes. The measurement was performed with an individual arm circumference adjusted bladder size and performed at the left upper arm. In addition, the norm values for the age group of children were also collected with the Mobil-o-Graph device. This data was published recently.[78]

The Mobil-o-Graph device is an oscillometric measurement tool. Several studies validated the device and therefore made it a reliable device for measuring central blood pressure.[78, 79] The central blood pressure is calculated by the algorithm of the device based on collected data of the peripheral wave form. Conclusions about arterial stiffness can be drawn with the values of the central blood pressure.

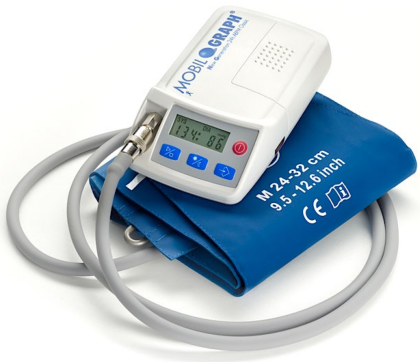


Figure 3: Mobil-o-Graph device of I.E.M (Germany)[80]

5.3.2 Metabolic Syndrome

The definition criteria of MetS for this study is based on the International Diabetes Federation,[24] but instead of fasting plasma glucose, increased $HbA1_c$ was used. The syndrome is diagnosed if at least three of the following risk factors are found: increased serum triglycerides, elevated blood pressure, decreased high-density lipoprotein, high $HbA1_c$, and visceral or central obesity. The risk factors and their conditions are displayed in Table 3.

Table 3: Risk factors of the Metabolic Syndrome and their conditions

Risk factor	Threshold	Examination
Waist circumference	♀ ≥ 102 cm / ♂ ≥ 88 cm (country-specific)[24]	Tape measure (inferior rib margin - superior border of the iliac crest)[81]
Triglycerides	≥ 150 mg/dl	Blood sampling was performed in non-fasting state and sitting position
or treatment for lipid abnormality	Yes	
HDL cholesterol	♀ ≥ 40 mg/dl / ♂ ≥ 50 mg/dl	
or treatment for lipid abnormality	Yes	
$HbA1_c$	≥ 5.7 %	
or previously diagnosed diabetes	Yes	
Blood pressure		cf. Chapter 2.5 Blood pressure and arterial stiffness
Systolic blood pressure	≥ 130 mmHg	
or diastolic blood pressure	≥ 85 mmHg	
or hypertensive therapy	Yes	

HbA1c: Hemoglobin A1c; HDL: High density lipoprotein

The use of $HbA1_c$ for the diagnosis of diabetes mellitus is recommended by the American Diabetes Association.[75] $HbA1_c$ values from 5.7% to 6.4% signified a “prediabetes” analogously to impaired fasting glucose or impaired glucose tolerance. A further study showed a $HbA1_c$ value greater or equal 5.7% concurs with fasting plasma glucose to determine MetS.[82] Therefore, the value of 5.7% was defined as risk factor for MetS.

5.3.3 Carotid intima-media thickness (cIMT)

The cIMT was measured with the ultrasound device GM-72P00A (Panasonic, Japan) at the A. carotis communis. Thereby, the guidelines of the Mannheim Carotid Intima-Media Thickness and Plaque Consensus were complied with.[46] For the measurement, the patients lied in the supine position and the head was turned 45° into a wedge pillow. The A. carotis communis was measured on both sides and in two angles respectively, on the right neck side at 120° and 150° and on the left side at 210° and 240°. In a longitudinal view, the A. carotis communis was analyzed one centimeter caudal of the bifurcation into the A. carotis interna and externa. The cIMT was calculated automatically by the ultrasound device over eight heart beats for each angle. The mean average of both sides was used for further calculations.

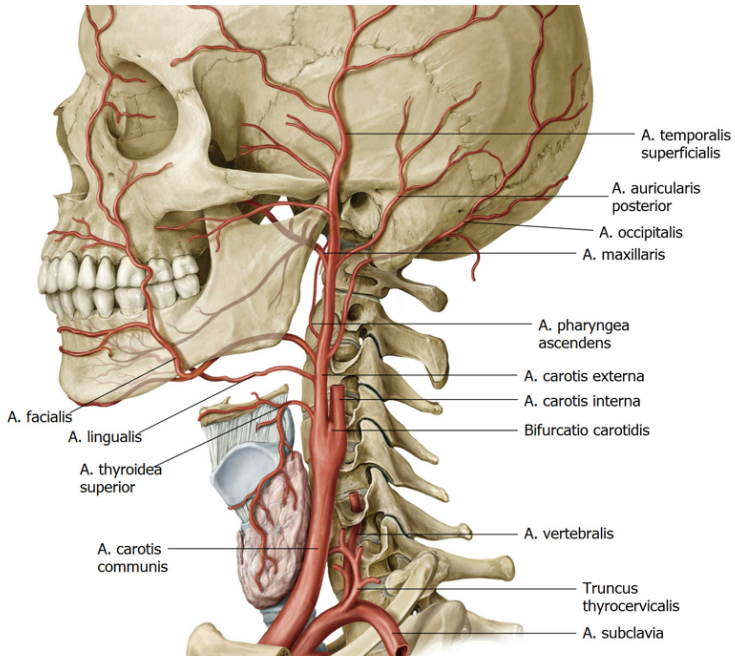


Figure 4: A. carotis communis on the left neck side[83]

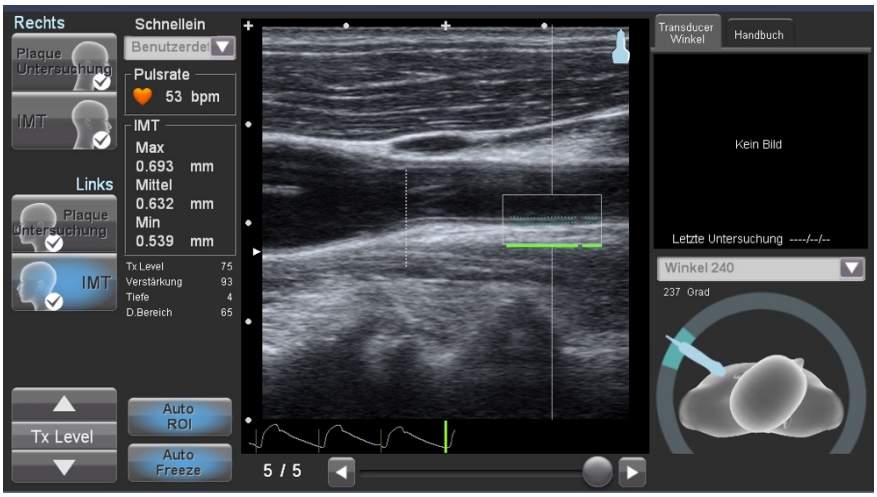


Figure 5: Ultrasound of the cIMT at A. carotis communis (longitudinal)

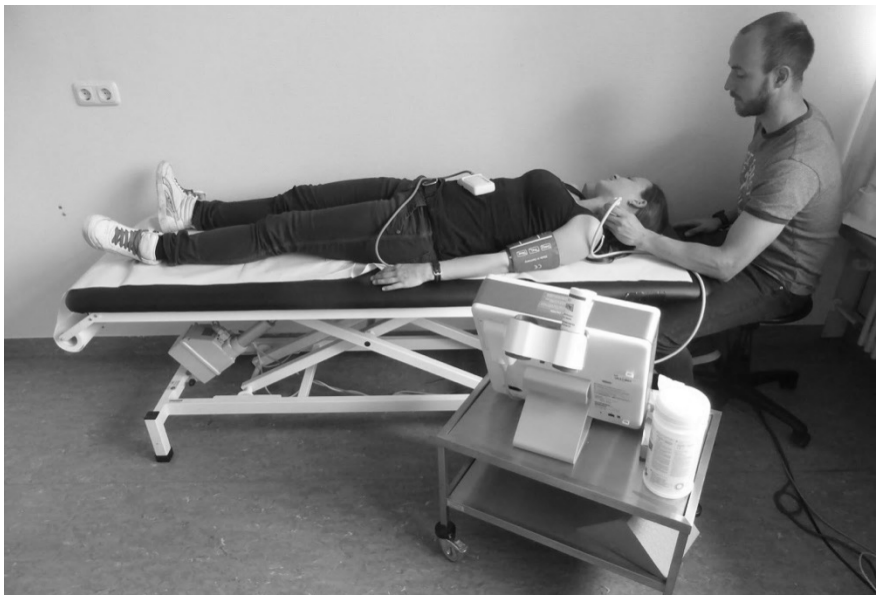


Figure 6: Study set-up during the measurement of blood pressure and carotid intima media thickness

5.3.4 Cardiovascular risk score

The cardiovascular risk was calculated with the PROCAM score. It reflects the risk of a fatal or non-fatal myocardial infarction or stroke percentile within the next 10 years. The score is based on a German reference cohort of 18,460 men and 8,518 women between 20-78 years followed for an average of 11.7 years.[84] The PROCAM score can be calculated in two ways: the PROCAM quick check or the PROCAM health check. The included risk factors of the different calculation methods are displayed in Table 4.

Table 4: Risk factors of the PROCAM quick and PROCAM health check

	PROCAM quick check	PROCAM health check
Age	✓	✓
Sex	✓	✓
Height	✓	–
Weight	✓	–
Systolic blood pressure	✓	✓
Diabetes type 2	✓	✓
Current smoking	✓	✓
Antihypertensive drug treatment	✓	–
Family history of cardiovascular event	✓	✓
LDL cholesterol	–	✓
HDL cholesterol	–	✓
Triglyceride	–	✓

HDL: High density lipoprotein; LDL: Low-density lipoprotein

Smoking status (yes/no, at the moment of measurement), hypertensive drug treatment (yes/no, at the moment of measurement), and the presence of a cardiovascular event of a first-degree family member before the age of 60 (yes/no) are risk factors that were collected with a questionnaire (cf. *Appendix D*). Blood sampling for the blood biomarkers was performed in a non-fasting state and sitting position at the German Heart Center.

In Figure 6 an example of calculating the risk of a fatal or non-fatal myocardial infarction or stroke with the PROCAM health check is given.

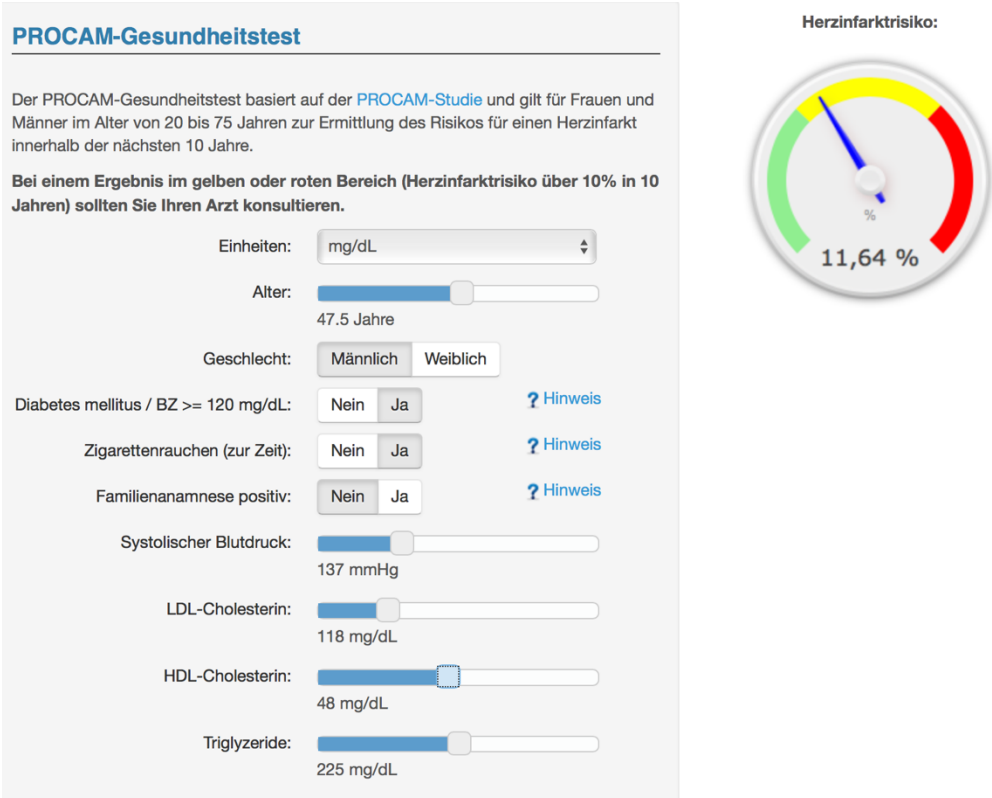


Figure 7: Example calculation with the PROCAM health check

For calculations follow this link: http://cmd-taskforce.org/risk-assessment/.

6 Publications

6.1 Increased arterial stiffness in children with congenital heart disease

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Individual contribution:

The PhD candidate is the main author of this paper. In cooperation with other examiners, she sampled the data at the German Heart Center. She performed the statistical analysis and presentation of the results. The manuscript was revised by Priv. Doz. Dr. rer. nat. Jan Müller. The final proof of the manuscript was done by Prof. Renate Oberhoffer, Prof. Hager and Prof. Ewert. The PhD candidate and Priv. Doz. Dr. rer. nat. Jan Müller went through the submission process until publication.

Abstract

Aims: Central systolic blood pressure (SBP) is a measure of arterial stiffness and strongly associated with atherosclerosis and end-organ damage. It is a stronger predictor of cardiovascular events and all-cause mortality than peripheral SBP. In particular, for children with congenital heart disease (CHD), a higher central SBP might impose a greater threat of cardiac damage. The aim of the study was to analyze and compare central SBP in children with CHD and healthy counterpart.

Methods and Results: Central SBP was measured using an oscillometric method in 417 children (38.9% girls, 13.0 ± 3.2 years) with various CHD between July 2014 and February 2017. The test results were compared to a recent healthy reference cohort (RC) of 1466 children (49.5% girls, 12.9 ± 2.5 years). After correction for several covariates in a general linear model, central SBP of children with CHD was significantly increased (CHD: 102.1 ± 10.2 vs. Healthy RC: 100.4 ± 8.6, p<.001). The analysis of CHD subgroups revealed higher central SBP in children with left heart obstructions (Mean Difference (MD): 3.6 mmHg, p<.001), Transpositions of the great arteries after arterial switch (MD: 2.2 mmHg, p=.017) and univentricular hearts after total cavopulmonary connection (MD: 2.1 mmHg, p=.015), compared to the reference.

Conclusion: Children with CHD have significantly higher central SBP compared to healthy peers, predisposing them to premature heart failure. Screening and long-term observations of central SBP in children with CHD seems warranted in order to evaluate the need for treatment.

Keywords: children, congenital heart disease, arterial stiffness, systolic blood pressure

Introduction

Central systolic blood pressure (SBP) is a surrogate measure of arterial stiffness that characterizes the vascular function to cushion forward and, from the periphery reflected, backward traveling pulse waves.[28] Increased central SBP has several negative effects as an earlier reflection of the backwards traveling wave imposes a greater afterload for the left ventricle. Consequences of those early-reflected waves are myocardial remodeling and a dysfunctional buffering function of the left ventricle.[85, 86] As a response to those hemodynamic changes, pulsatile pressure raises and leaking microcirculation impairs the perfusion of brain, eyes and kidneys.[85, 87] In front of that pathophysiological background, it is not surprising that an augmented central SBP is strongly associated with atherosclerosis and end-organ damages[88] and outperforms the prognostic value of peripheral SBP as a predictor of cardiovascular events and all-cause mortality.[67, 88]

In patients with congenital heart disease (CHD), surgical improvement and aftercare treatment tremendously increased live expectancy within the last decades.[6] Among others, cardiovascular long-term morbidity and mortality had therefore become of clinical significance to avoid that success in lowering mortality is paid with higher morbidity in the nearer future.[89] Indeed several studies have suggested higher arterial stiffness or lower elastic properties of the vasculature already in children with CHD.[29-33] Unfortunately, all of them used different methodologies, focused on single diagnostic sub- and age-groups making a comparison within various CHD impossible.

Thus, the aim of this study was a comprehensive approach to analyze central SBP in children with various CHD and to compare these patients to a healthy reference cohort. Further, central SBP was analyzed within the CHD subgroups to identify vulnerable subgroups at higher risk.

Patients and Methods

Study subjects

In a cross-sectional design, arterial stiffness was analyzed in 417 children with various CHD (38.9% girls, 13.0 ± 3.2 years) aged 6 to 18 years at the outpatient department of the German Heart Center in Munich between July 2014 and February 2017. All children were recruited from a regular outpatient visit, were in NYHA class I or II, had no mental developmental delays, evident disabilities or syndromes.

Children with CHD were compared to a recent healthy reference cohort (RC) of 1466 children (49.5% girls, 12.9 ± 2.4 years) analyzed from October 2012 to July 2013 in several Bavarian schools. The data on the reference values for central SBP in healthy children was recently published.[78] Body mass index values were transformed into z-scores according to German reference values from Kromeyer-Hauschild et al..[90]

The various CHDs were classified into five major subgroups: “left heart obstruction” including aortic stenosis and coarctation of the Aorta, “right heart obstruction” including Tetralogy of Fallot and Pulmonic Stenosis, “isolated shunts” including atrial/ventricular/ atrioventricular septal defect, “transposition of the great arteries after arterial switch” and children after ”Total-pulmonary connection”. Figure 1 shows the selection of the patients and the CHD subgroup classification.

The accordance of the Declaration of Helsinki (revision 2008) and the Good Clinical Practice Guidelines were the basis of this study. The study was approved by the ethical board of the Technical University of Munich (project number: 314/14). All children and their guardians gave written informed consent.

Measurement of central SBP

Arterial stiffness was analysed in both, children with CHD and healthy controls, by pulse wave analysis using the Mobil-o-Graph device of I.E.M (Germany), which is an oscillometric measurement tool. Validation of the Mobil-o-Graph by

several studies makes it a reliable measurement device of central SBP. The algorithm of the device calculates the central SBP based on the measures of the peripheral wave form.[78, 79] The measurement was performed at the left upper arm after lying in supine position for five minutes. The bladder size was adjusted for individual arm circumference.

Data analysis

Descriptive data of the children with CHD and the RC are shown in mean values and standard deviation (mean ± SD). Differences in anthropometric data were analyzed with a t-test for unpaired samples. Due to diverse anthropometric data within the groups, a general linear model was fit to the data. That is a generalization of linear regression by considering more than one independent variable with Bonferroni post-hoc test within the diagnostic subgroups. Independent covariates entered to adjust for confounding were age, sex, body mass index, peripheral mean arterial pressure (pMAP), heart rate, and the intake of hypertensive agents (yes/no). Mean difference [91] compared to the healthy RC was calculated.

All analyses were conducted with SPSS (version 23.0, IBM Corporation) and the level of significance was set to a p-value <.050 for all tests.

Results

Significant differences in children with CHD and the RC were observed in sex ($p<.001$), BMI z-score ($p<.001$), and peripheral SBP ($p=.047$), as demonstrated in Table 1. Detailed overview of the diagnostic subgroups is presented in Table 2

Despite a slightly lower peripheral SBP, children with CHD had a significantly increased central SBP compared to the RC (CHD: 102.1 ± 10.2 vs. Healthy RC: 100.4 ± 8.6, $p<.001$) after controlling for confounders age, sex, body mass index, mean arterial pressure, heart rate, and intake of hypertension medication.

Figure 2 shows that after correction for the same covariates, the analysis of CHD subgroups resulted in significantly higher central SBP in children with left heart obstructions (MD: 3.6 mmHg, $p<.001$), TGA after arterial switch (MD: 2.2 mmHg, $p=.017$), univentricular heart after total cavopulmonary connection (TCPC) (MD: 2.1 mmHg, $p=.015$) and the miscellaneous group (MD: 1.9 mmHg, $p=.003$), compared to healthy RC. There was no difference between RC and the right heart obstructions and isolated shunts.

Discussion

The results of this study show that children with CHD have significantly higher arterial stiffness compared to a healthy reference cohort. Within the diverse CHD subgroups, significantly higher arterial stiffness was present in subjects with left heart obstructions, TGA after arterial switch and univentricular hearts after TCPC.

In recent years', measurement and understanding of arterial stiffness becomes a major interest in patients with CHD. Up to now, several studies have outlined in different subgroups of patients with CHD by different means that arterial stiffness is increased and the buffering function of the vasculature impaired.[29-33] Genetic aortic wall abnormalities in the media layer of the great vessels, in collagen, elastin and the structure of smooth muscle cells impair the natural buffering function of the vessels in general.[29] Surgical scars and implanted external materials like patches and conduits that are stiffer than native tissue alter pulse wave reflection as well.[92] Surgery is also the putative culprit for autonomic nervous dysfunction, a major blood pressure control mechanism. Numerous studies have assessed that fact either by baroreflex sensitivity or by means of heart rate variability in Fontan,[93-95] patients with TGA[96, 97] and coarctation of the aorta.[98-100] Also injuries of the vasa vasorum[31] and aortopulmonary shunt in conjunction with aortic root dilatation[101, 102] are additional factors associated with higher arterial stiffness.

In addition, modifiable risk factors like overweight can contribute to early vascular stiffening. The negative effect on central SBP of the body weight was previously demonstrated in 320 healthy children and adolescents by Müller and colleagues.[103] They pointed out the necessity of overweight prevention in children to lower stiffening of the arteries. These recommendations are transferable to children with CHD since recent studies demonstrated that children and adolescents with CHD tend to experience overweight and obesity problems rather than being underweight.[104]

In accordance to other reports, the stiffest vessels were detected in children with left heart obstructions.[30, 79, 87, 105] In patients with coarctation of the aorta reduced elasticity of the prestenotic region was observed already in infants and that pathology could not be resolved after surgery incorporating a genetic component.[106, 107] Also baroreceptors in the upper vascular bed might be impaired and tolerating a higher pressure that results in premature arterial stiffness.[32, 100, 108] In patients with aortic stenosis impairment in elastic properties were found [30] and other reports recently showed that also children with well-functioning bicuspid aortic valves had abnormal aortic elasticity and diastolic function.[109]

Even in children with TGA after arterial switch higher arterial stiffness was detected.[31, 97, 102, 110, 111] Although anatomic correction in infancy restores the circulation, the anatomic pulmonary valve and a proximal pulmonary trunk remain interposed between the left ventricle and the ascending aorta. The post-surgical sharper angulation of the neo-aorta and aortic arch has shown to be associated with early pulse wave reflection.[111, 112] In addition to native wall abnormalities, after experimental surgical denuation of the aorta in animals, structural changes and stiffening of the aortic wall were observed. This indicates damages of the vasa vasorum.[113, 114] Voges et al. further assumed impeded aortic distensibility in patients after arterial switch operation by fibrosis around the transposed arteries or the pulmonary artery branches embracing the aorta after Lecompte maneuver.[102]

Finally, also children with TCPC emerged to be associated with higher risk, an observation that was made in several other reports.[30, 115, 116] Especially in children with hypoplastic left heart syndrome the aortic arch reconstruction with patches indicated to results per se in reduced distensibility of the ascending aorta.[117] Also unfavorable ventriculo-arterial coupling and consequent reduced mechanical efficiency may contribute.[118] Further, Tomkiewicz-Pajak et al.[119] de-

scribed a positive association between higher arterial stiffness and age at surgery in patients after Fontan procedure. This association might be explained by the fact that volume overloading contribute to arterial stiffness in patients with univentricular heart in the first few months after partial cavopulmonary connection.[120]

Independent of the reason, arterial stiffness at an early age, predisposes children with CHD to premature cardiac damage and vascular remodeling. Subsequent arterial hypertension and increased afterload are just two consequences and tremendous burden for the systemic ventricle. According to the generated percentile curves from Elmenhorst and colleagues[78] an increase of 3.6 mmHg in central SBP, as found in patients with left heart obstructions, results in a shift from the 50th to the 75th percentile. This emphasizes that at least some CHD are associated with arterial stiffness and therefore at increased risk for future cardiovascular disease. Early evaluation of cardiovascular risk and early prevention are warranted.

Conclusion

Children with CHD have significantly higher central SBP compared to healthy peers predisposing them to premature atherosclerotic cardiovascular diseases and heart failure. Long-term observations of central SBP in children with CHD are necessary in order to evaluate the need for prevention and early treatment.

Limitations

In this study, only a single pulse wave analysis to estimate central SBP was conducted. For a more accurate measurement and to confirm the recent findings, repeated measurement should be considered. However, the study protocol was similar in the patients with CHD and in the healthy RC, which controls for a systematic error in both groups by this huge sample size. In addition, healthy children are not familiar to blood pressure measurements and the resulting tension may lead to higher values. For this reason, the central SBP difference between children with CHD and the RC in this study might be underestimated. Moreover, the study lacks corrections for other covariates like diet, genetic factors and smoking that were not assessed in the study but have shown to be associated with measures of arterial stiffens. Finally, our institution is a specialized tertiary center and the more severe and complex lesions might therefore be overrepresented.

Funding

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Acknowledgment

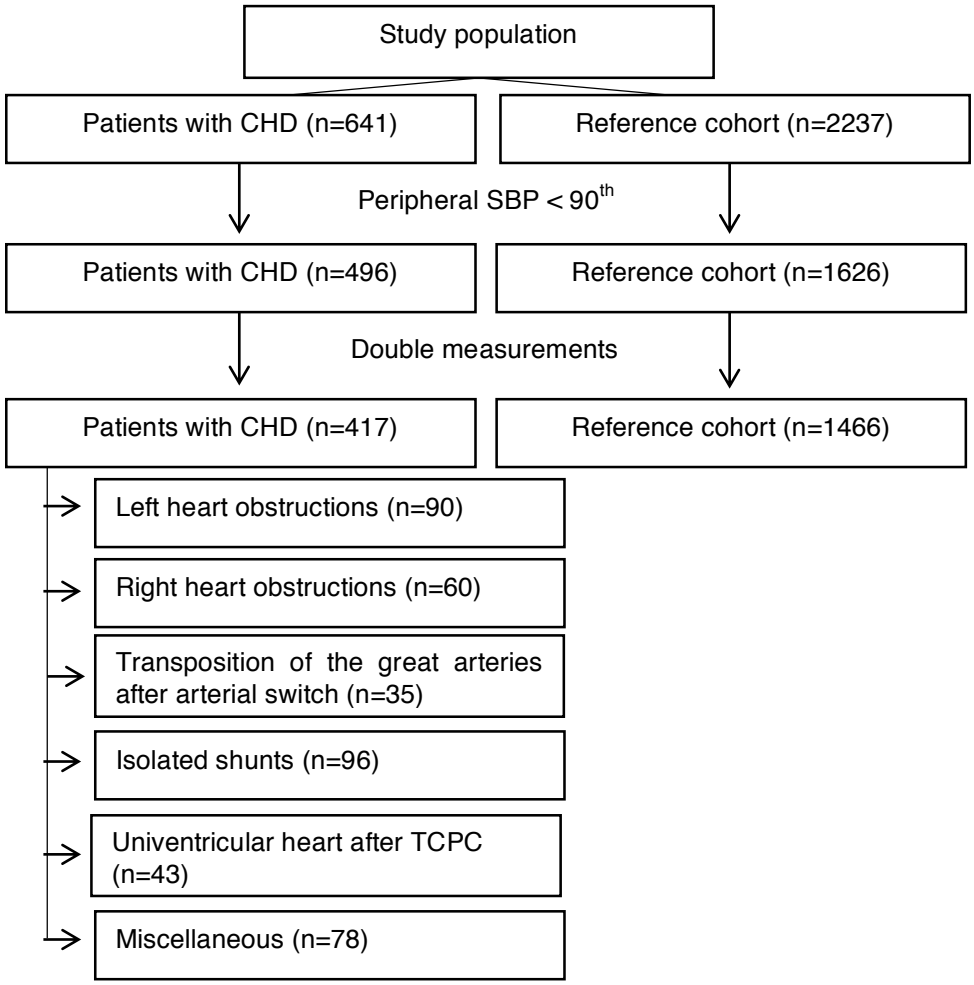
No conflicts of interest.

Authorship

ALH and BR sampled the data in the study center. ALH also analyzed the data and drafted the first version of the manuscript. JM was responsible for conception and design of the study and was responsible for data monitoring and integrity. RO, AH and PE contributed to design and conception of the study. All authors gave important input for revising and improving the quality of the manuscript and approved the final version of the manuscript.

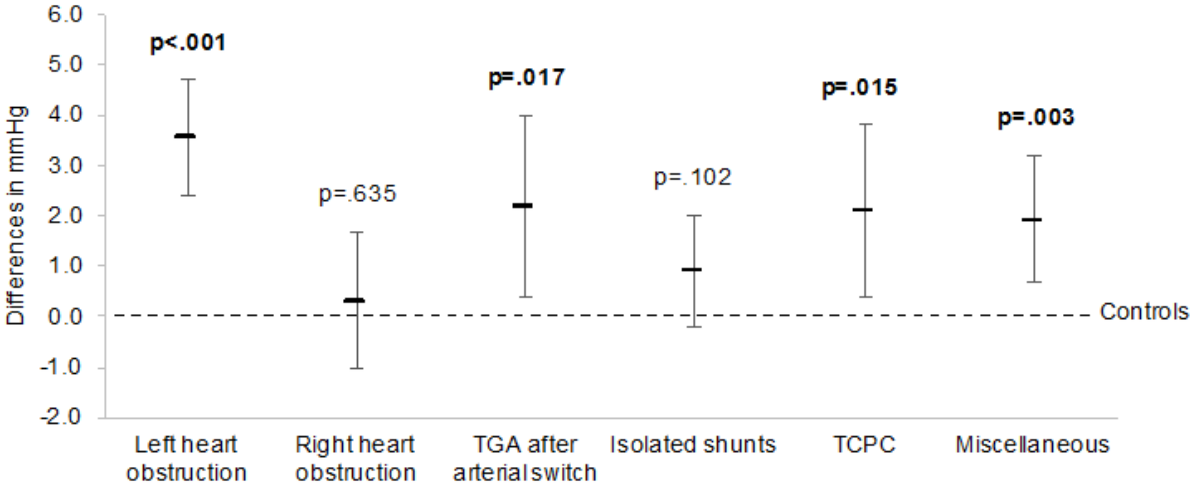
Figures

Figure 1: Study population, selection of the patients and CHD subgroup classification



CHD: congenital heart disease, SBP: systolic blood pressure, TCPC: total cavopulmonary connection

Figure 2: Mean difference of central systolic blood pressure for children with congenital heart disease compared to the healthy reference cohort, corrected for age, sex, body mass index, heart rate, peripheral mean arterial pressure and the intake of hypertensive agents.



TCPC: total cavopulmonary connection, TGA: Transposition of the Great Arteries

Tables

Table 1: Anthropometric data of children with congenital heart disease and the reference cohort

	Patients with CHD (n=417)	Controls (n=1466)	p-value
Sex (female)	167 (38.9%)	726 (49.5%)	**<.001**
Age (years)	13.0 ± 3.2	12.9 ± 2.4	.760
Height (cm)	155.7 ± 18.8	156.8 ± 13.5	.238
Weight (kg)	47.5 ± 16.9	48.5 ± 14.3	.246
BMI z-score	-0.19 ± 1.2	0.41 ± 1.0	**<.001**
pSBP (mmHg)	112.7 ± 9.4	113.7 ± 7.6	**.047**
pDBP (mmHg)	65.7 ± 7.6	65.8 ± 7.3	.712
pMAP (mmHg)	87.2 ± 7.4	87.8 ± 6.3	.158
cSBP (mmHg)	102.1 ± 10.2	100.4 ± 8.6	**.001**

cSBP: central systolic blood pressure, BMI: body mass index, pMAP: peripheral mean arterial pressure, pDBP: peripheral diastolic blood pressure, pSBP: peripheral systolic blood pressure, mean ± standard deviation, significance value was set to .05

Table 2: Anthropometric data of children with congenital heart disease according to diagnostic subgroups

	Sex (female)	Age (Years)	BMI z-score	pSBP (mmHg)	pDBP (mmHg)	pMAP (mmHg)	cSBP (mmHg)
Left Heart Obstruction (n=90)	24 (26.7%)	13.0 ± 3.0	-0.09 ± 1.33	110.9 ± 11.0	64.9 ± 7.2	85.9 ± 7.4	103.0 ± 10.9
Right Heart Obstruction (n=60)	25 (41.7%)	13.2 ± 3.0	-0.17 ± 1.22	113.7 ± 8.8	67.4 ± 7.7	88.7 ± 7.4	102.1 ± 9.9
TGA after arterial Switch (n=35)	9 (25.7%)	12.9 ± 3.8	+0.07 ± 1.16	114.4 ± 10.5	65.2 ± 7.5	87.9 ± 8.1	103.8 ± 11.9
Isolated Shunt (n=96)	47 (49.0%)	12.8 ± 3.5	-0.15 ± 1.11	113.1 ± 8.9	65.9 ± 7.1	87.6 ± 7.1	101.5 ± 9.4
TCPC (n=43)	14 (32.6%)	12.6 ± 3.2	-0.39 ± 0.90	113.2 ± 8.3	65.5 ± 8.7	87.3 ± 7.7	101.3 ± 8.9
Miscellaneous (n=78)	37 (47.4%)	12.9 ± 3.3	-0.32 ± 1.44	112.5 ± 8.8	65.9 ± 7.9	85.9 ± 7.4	101.8 ± 10.6

TCPC: total cavopulmonary connection, TGA: Transposition of the Great Arteries, cSBP: central systolic blood pressure, BMI: body mass index, pMAP: peripheral mean arterial pressure, pDBP: peripheral diastolic blood pressure, pSBP: peripheral systolic blood pressure, mean ± standard deviation, significance value was set to .05

6.2 Metabolic Syndrome in Adult Patients with Congenital Heart Disease is associated with Increased Carotid Intima-Media Thickness

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Individual contribution:

The PhD candidate is the main author of this paper. She sampled the data at the German Heart Center, performed the statistical analysis of the results, and the presentation of the results. The manuscript was revised by Priv. Doz. Dr. rer. nat. Jan Müller. The final proof of the manuscript was done by Prof. Renate Oberhoffer, Prof. Hager and Prof. Ewert. The PhD candidate and Priv. Doz. Dr. rer. nat. Jan Müller do the submission process and the paper is under review in Atherosclerosis.

Abstract

Aims: Age-related cardiovascular diseases are a relevant risk in the aging population of adults with congenital heart diseases (ACHD). Risk factors such as metabolic syndrome (MetS) and carotid intima-media thickness (cIMT) increase the risk of cardiovascular diseases. The aim of the study was to assess MetS in ACHD and outline a possible association to cIMT.

Methods and Results: In total, 434 ACHD (43.8 ± 9.6 years, 50.5% female) were screened for MetS by the standards of the International Diabetes Federation and cIMT by ultrasound from January 2017 to July 2018. MetS was prevalent in 14.3% of the ACHD population whereby 27 (12.3%) female ACHD and 35 (16.3%) male ACHD were affected. Among the severity classes, simple forms of CHD had a MetS prevalence of 9.7%, moderate 19.4% and severe 14.7%. ACHD with MetS had significantly increased cIMT compared to ACHD without MetS (ACHD with MetS: 0.560 ± 0.087 mm, ACHD without MetS: 0.592 ± 0.077 mm, mean difference: 0.032 mm, p=.007). Such a difference in vascular structure corresponds to roughly six years of normal vascular aging of the vessels.

Conclusion: ACHD with MetS have a thicker cIMT compared to ACHD without MetS. Screening for MetS and targeting risk factors in ACHD might help to prevent structural alterations of the vessels at an early stage.

Keywords: Congenital heart disease, metabolic syndrome, carotid intima-media thickness

Introduction

As a consequence of an improved outcome, long-term exposure to cardiovascular risk factors has increased in adults with congenital heart disease (ACHD), making cardiovascular diseases a relevant topic for these patients and their physicians nowadays.[53, 121, 122]

The metabolic syndrome (MetS) is a cluster of at least three of the following risk factors: visceral or central obesity, high serum triglycerides, elevated blood pressure, low high-density lipoprotein, and increased fasting plasma glucose. It is a frequent metabolic disorder and a crucial public-health challenge [40], which - depending on the definition criteria - 10-40% of people suffer from worldwide.[41] Underlying risk factors for MetS are physical inactivity, age, unhealthy diet with high amounts of saturated fat, cholesterol, as well as simple sugar and hormonal imbalance.[23] Consequences of MetS are triggered amongst others by elevated levels of pro-inflammatory markers and activated sympathetic nervous and renin-angiotensin system leading to pathophysiologic changes as atherosclerosis and vascular calcification.[44] MetS is therefore a major risk factor for age-related cardiovascular diseases and diabetes type 2,[23, 24] and associated with an increased cardiovascular and all-cause mortality and morbidity.[24, 39, 123, 124] Unfortunately, there is evidence that the prevalence of MetS is higher in ACHD than in healthy controls.[42, 43]

By examining the carotid intima-media thickness (cIMT), possible pathophysiological changes at the vessels become visible. cIMT is a surrogate end point of cardiovascular outcomes in clinical studies [46] and therefore a risk factor for cardiovascular diseases,[125, 126] and is further associated with the risk of cognitive impairment.[127]

So far, the association of atherosclerotic and vascular proliferation due to the MetS on carotid intima-media thickness (cIMT) in ACHD is not clear. Hence, the aim of the study was to examine whether MetS is a possible driver of cIMT proliferation. Therefore, MetS and cIMT were assessed in ACHD and the cIMT was compared between ACHD with and without MetS.

Patients and Methods

Study subjects

From January 2017 to July 2018, 434 ACHD aged 30 years and older (43.8 ± 9.6 years, 50.5% female) were prospectively examined at the German Heart Center in Munich for several cardiovascular risk parameters. The patients with various types of CHD had a routine follow-up at the outpatient clinic.

All ACHD were grouped by their congenital diagnosis and the surgical correction into eleven CHD subgroups. The number of patients in each subgroup, severity class according to Warnes and colleagues [128], and the prevalence of MetS are displayed in table 1.

The local ethical board of the Technical University of Munich approved the study (project number: 64/17S) which is part of the CARING (Cardiovascular Risk in grown-up congenital heart disease) project which is registered in the 'Deutsches Register Klinischer Studien' with the number DRKS00015248. Written informed consent was signed by all patients.

Metabolic Syndrome (MetS)

MetS was defined by the criteria of the International Diabetes Federation [24] with the only adaption of haemoglobin $A1_c$ ($HbA1_c$) instead of fasting plasma glucose. Metabolic syndrome was defined as existent when the patient met three or more of the following criteria which are also displayed in table 2:

Waist circumference was measured using a non-stretchable tape, placed horizontally midway between the inferior rib margin and the superior border of the iliac crest according to the World Health Organization and the International Diabetes Federation.[81] Population- and country-specific values for Caucasian were a waist circumference of 102 cm for men and 88 cm in women.[24]

Blood pressure was measured using the oscillometric measurement device Mobil-o-Graph (I.E.M, Stolberg, Germany) in all ACHD. Therefore, the patients rested in supine position for five minutes. With an arm-adjusted cuff size, the blood pressure was measured at the left upper arm. History of hypertension,

systolic blood pressure, 130 mmHg or higher or a diastolic blood pressure of 85 mmHg or any hypertensive treatment was considered as meeting the criteria for MetS.

Triglycerides, HDL cholesterol and $HbA1_c$ were drawn from an antecubital vein in sitting position in a non-fasting state according to the recommendations of the European Atherosclerosis Society.[129] To analyse the blood probes the assay of Roche with the analyser module cobas c 501 was used. ACHD with treatment for lipid abnormality or triglycerides of 150 mg/gl or higher met the triglyceride criteria. MetS criteria in women were HDL cholesterol <40mg/dl and in men <50mg/dl cholesterol.

As already mentioned, fasting plasma glucose was substituted by $HbA1_c$ for defining MetS. The American Diabetes Association [130] recommends the use of the $HbA1_c$ test for the diagnose of diabetes mellitus. A value ranging from 5.7% to 6.4% of $HbA1_c$ defines individuals at a high risk of diabetes. The term "prediabetes" could also be applied to these people analogously with impaired fasting glucose or impaired glucose tolerance. Additionally, studies have shown that good agreement exists between $HbA1_c$ and fasting plasma glucose in determine MetS.[131] Therefore, a value of 5.7% or higher was considered meeting the MetS criteria.

Carotid intima-media Thickness (cIMT)

The cIMT was measured at the A. carotis communis on both sides of the neck in two angles respectively and assessed in a longitudinal view with the ultrasound device GM-72P00A (Panasonic, Japan). The measurement was performed in accordance with the Mannheim Carotid Intima-Media Thickness and Plaque Consensus and is therefore justified as a reliable marker for cardiovascular risk.[46] All patients lied in supine position and turned their head for the ultrasound into a wedge pillow with 45°. The measuring angles on the right neck side were 120° and 150° and on the left side 210° and 240°. Measuring point at the A. carotis communis was one centimeter caudal of the bifurcation into the A.

carotis interna and externa. The device automatically calculated the cIMT over eight heart beats for each angle. For statistical analysis, the mean of these four measurements was calculated.

Data analyses

Anthropometric data of the ACHD is illustrated as mean values and standard deviations. Differences concerning anthropometric data between ACHD with and without MetS were analyzed with a t-test for unpaired samples. By performing a general linear model, differences for the IMT between ACHD with and without MetS were calculated while adjusting for age and sex. Calculations were performed with SPSS (version 23.0, IBM Corporation) with a level of significance of <.05 for all tests. Figures were created with R Studio (version 1.1.423).

Results

MetS was prevalent in 62 (14.3%) of the ACHD. In female ACHD 27 (12.3%) and in male ACHD 35 (16.3%) had a MetS. Among the severity classes according to Warnes and colleagues [128], simple forms of CHD had a MetS prevalence of 9.7%, moderate 19.4% and severe 14.7%.

Concerning the single risk factors, waist circumference was increased in 91 (21.9%), blood pressure in 264 (60.8%), triglycerides in 113 (26.0%), HDL in 62 (14.5%) and diabetes mellitus was prevalent in 23 (5.6%). ACHD with MetS had a significantly higher waist circumference than the ACHD without MetS (ACHD with MetS: 101.6 cm, ACHD without MetS: 84.0 cm, p<.001), triglycerides were significantly higher in ACHD with MetS (ACHD with MetS: 193.3 mg/dl, ACHD without MetS: 108.1 mg/dl, p<.001) and decreased HDL values were found in ACHD with MetS (ACHD with MetS: 44.1 mg/dl, ACHD without MetS: 62.1 mg/dl, p<.001). Greater values in $HbA1_c$ were significantly more frequent in ACHD with MetS than in ACHD without MetS (ACHD with MetS: 5.4%, ACHD without MetS: 5.1%, p<.001). Systolic blood pressure (ACHD with MetS: 125.2 mmHg, ACHD without MetS: 119.8 mmHg, p<.001) as well as the diastolic blood pressure (ACHD with MetS: 79.4 mmHg, ACHD without MetS: 74.1 mmHg, p=.005) was significantly increased in ACHD with MetS (Table 3, Figure 2).

The cIMT was significantly increased in ACHD with MetS compared to ACHD without MetS (ACHD with MetS: 0.560 ± 0.087 mm, ACHD without MetS: 0.592 ± 0.077 mm, mean difference: 0.032 mm, p=.007) (Table 3, Figure 1). This difference corresponds to 5.6 years of normal vascular aging between ACHD with and without MetS.

Discussion

ACHD patients with MetS had a detrimental vascular structure by means of cIMT compared to patients without MetS. That change in vessel structure roughly corresponds to six years of normal vascular aging of the vessels.

In this study, 14.3% of the ACHD patients were diagnosed with a MetS, which seems slightly lower compared to 21.5% of the 40-49 year old cohort of the population-based sample in Germany.[132] In contrast, the study of Deen and colleagues demonstrated 15.0% of the ACHD patients had a MetS and the prevalence was twice as high as in the population-based sample.[42] Among the severity classes according to Warnes and colleagues [128] in this study, simple forms of CHD had a MetS prevalence of 9.7%, moderate 19.4% and severe 14.7%. In comparison to Deen and colleagues [42], who subcategorized the ACHD into simple (simple complexity) and complex (moderate and great complexity), the prevalence within the subgroups was similar to this study as simple forms had a prevalence of 13.6% and complex CHD's 15.7%.

However, the diagnosis of MetS is complicated because it strongly depends on the applied MetS' definition and therefore a comparison among the different studies is difficult. Reinehr and colleagues reported a varying prevalence of MetS ranging from 6-39% depending on eight different MetS definitions.[133] It is also questionable whether the criteria of MetS can be compared directly between the normal population and the population of ACHD. No study has prospectively evaluated these five risk factors in ACHD with regard to mortality and morbidity so far, but in HIV patients it was shown that risk scores barely predict the estimated risk of cardiovascular events.[134] Another argument for this consideration is that several studies found decreased insulin sensitivity, abnormal glucose tolerance and low high-density lipoprotein levels in ACHD cohort.[42, 55, 58] A recent study further suggest a different lipid metabolism in cyanotic patients as seen in low LDL and total cholesterol levels.[58] Furthermore, a lower fasting

blood glucose but higher $HbA1_c$ level and postprandial blood glucose were observed by Ohuchi and colleagues in postbiventricular and Fontan patients.[55] Given this context that metabolism in general might be different in this population, it makes sense to focus on different aspects within the examined cohort instead of comparing the data of CHD to healthy controls.

MetS is a key driver of arteriosclerosis and vascular damage can easily be assessed by ultrasound of the cIMT. In this study, ACHD with MetS had detrimental vessel structure in comparison to ACHD without MetS. The cIMT of ACHD with MetS was 0.032 mm higher compared to ACHD without MetS. Normal vascular aging is characterized by an increase of the cIMT by 0.0057 mm per year [135] which is equivalent to an age difference of 5.6 years between ACHD with and without MetS in this study. This vascular age difference is particularly critical because of the young age of the cohort. Progression of arteriosclerosis develops exponential instead of linear with increasing age. A presumption is that as this cohort ages, the difference in cIMT between the groups increases, and with it the biological age of the vessels, causing ACHD with MetS to tend towards a premature onset of cardiovascular events. A systematic review reported that a cIMT difference of 0.1 mm was related to a 10%-15% risk of myocardial infarction and 13%-18% risk of stroke.[136] Moreover, it cannot be ruled out that even a small thickening of the vessels as demonstrated in this study might lead to an increased risk of myocardial infarction or strokes in ACHD. Much more alarming, having MetS already in childhood turned out to be associated with a 12%-61% increased risk of high cIMT 15-25 years later.[137] However, it should be noted that an increase in cIMT not simply correlates with cardiovascular event prediction. Big cohort studies question the merit of cIMT progression and cardiovascular risk in the general population.[126, 138] Nevertheless, cIMT measurements slightly refined Framingham Risk Score for 10-year risk prediction of first-time myocardial infarction or stroke and is still a well accepted parameter for cardiovascular morbidity and mortality.[126]

All these facts indicate that MetS may accelerate changes in the vascular structure and elevates risk for cardiovascular diseases and thereby also affects ACHD. It might therefore be necessary to screen for MetS in ACHD as previously also mentioned by Deen and colleagues [42] and especially in those ACHD already having cardiovascular risk factors, as the risk of secondary diseases might be also increased in ACHD.

Conclusion

ACHD with MetS have a significantly higher cIMT compared to ACHD without MetS. Screening for MetS and its single risk factors in ACHD might help to prevent structural alterations of the vessels at an early stage.

Limitations

Lipid samples were drawn in a non-fasting state. Even though the European Atherosclerosis Society recommends that non-fasting blood samples should routinely be used for the assessment of plasma lipid profiles, it also represents a possible bias for the triglyceride assessment.[129] Blood pressure was determined only once, which can lead to inaccuracies and bias the criterion for MetS. Many patients with ACHD were prescribed ACE inhibitors, diuretics or beta-blocker without indication of hypertension. This could have led to an overestimation of the risk factor “blood pressure” and MetS in general. Nevertheless, it has to be assumed that this agent has its lowering hemodynamic effect on blood pressure and therefore also a lowering of cardiovascular risk.

The patient collection included in this study does not cover the entire patients of the outpatient clinic and the majority of patients have severe forms of CHD as the German Heart Centre in Munich is a specialized center for CHD. As a result, the distribution of CHD severity in this study might not reflect the distribution of CHD in the usual population.

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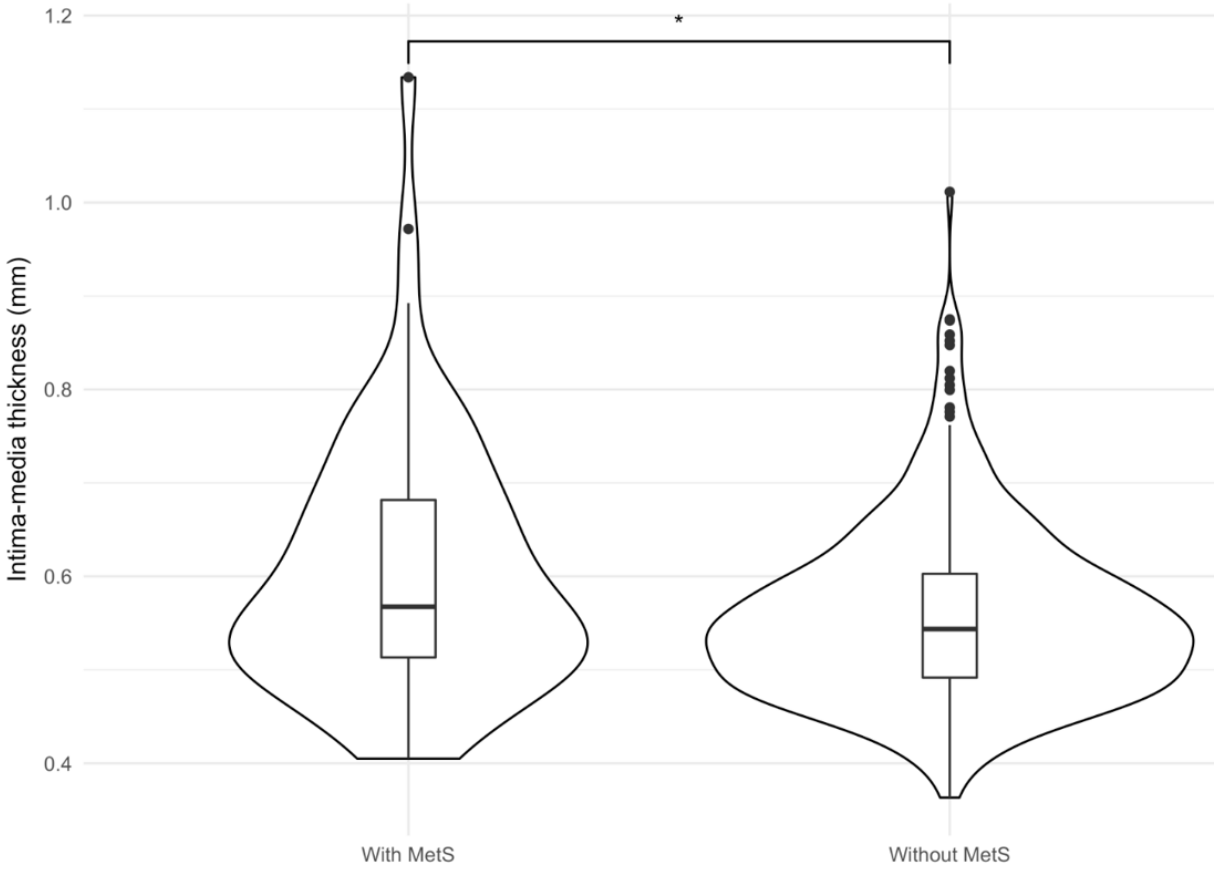
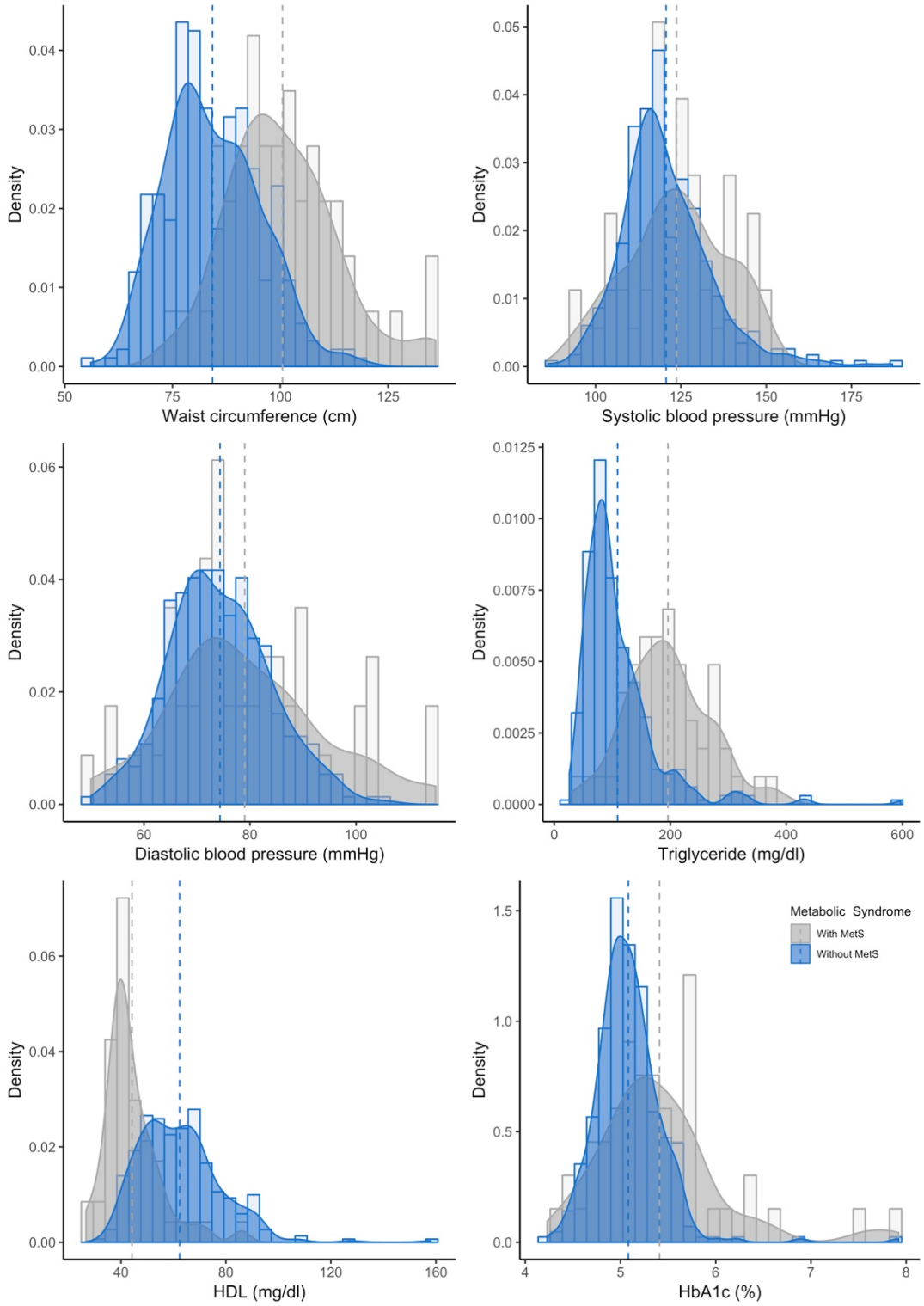
Figures

Figure 1: ACHD with MetS and without MetS and their intima-media thickness



MetS: Metabolic syndrome

Figure 2: ACHD with MetS and without MetS and the distributions of the single risk factors



ACHD: Adults with Congenital Heart Disease, HbA1c: Hemoglobin $A1_c$ HDL: High Density Lipoprotein, MetS: Metabolic syndrome

Tables

Table 1: ACHD subgroups and severity classes and the prevalence of MetS

		Subgroups	
	n	**Prevalence of MetS (%)**	**Age (years)**
Aortic stenosis	41	9.8	42.8 ±9.4
Coarctation of the aorta	38	21.1	41.0 ± 14.8
Cyanotic patients (native or palliated)	25	24.0	47.1 ±8.9
Ebstein anomaly	21	14.3	48.6 ± 12.8
Fontan circulation	17	17.6	40.5 ± 6.2
Isolated shunts*	84	15.5	47.2 ±11.3
Pulmonary stenosis	16	18.8	45.2 ±14.8
Tetralogy of Fallot	82	9.8	42.7 ±8.0
TGA after Rastelli repair§	23	13.0	42.7 ±10.4
TGA after Senning or Mustard	52	11.5	39.8 ±4.4
Others	35	14.3	44.9 ±9.8
		Severity class[1]	
	n	**Prevalence of MetS (%)**	**Age (years)**
Simple	62	9.7	48.2 ±11.9
Moderate	129	19.4	43.5 ± 9.7
Severe	230	14.7	42.7 ±8.6

TGA: Transposition of the Great Arteries

*including atrial, ventricular, and atrioventricular septal defect, §including congenital corrected Transposition of the Great Arteries

[1]Severity classes according to Warnes and colleagues [128]

Table 2: Definition criteria for the metabolic syndrome

	Female	**Male**
Waist circumference	≥ 102 cm	≥ 88 cm
Triglycerides	≥ 150 mg/dl	≥ 150 mg/dl
or treatment for lipid abnormality	Yes	Yes
High density lipoprotein (HDL)	≥ 40 mg/dl	≥ 50 mg/dl
or treatment for lipid abnormality	Yes	Yes
Blood pressure		
Systolic blood pressure	≥ 130 mmHg	≥ 130 mmHg
or diastolic blood pressure	≥ 85 mmHg	≥ 85 mmHg
or hypertensive therapy	Yes	Yes
Hemoglobin A1c (HbA1c)	≥ 5.7 %	≥ 5.7 %
or previously diagnosed diabetes	Yes	Yes

Table 3: ACHD with and without MetS and cIMT

		Anthropometric data		
	n	**ACHD with MetS (n=62)**	**ACHD without MetS (n=372)**	**p-value***
Age (years)	434	45.7 ± 9.6	43.5 ± 9.6	.091*
BMI	434	29.0 ± 4.8	24.4 ± 3.5	**<.001***
Waist circumference (cm)	434	101.6 ± 12.5	84.0 ± 10.9	**<.001***
Systolic BP (mmHg)	434	125.2 ± 14.3	119.8 ± 13.4	**.005***
Diastolic BP (mmHg)	434	79.4 ± 14.5	74.1 ± 9.7	**<.001***
		Blood lipids		
		ACHD with MetS (n=62)	**ACHD without MetS (n=372)**	**p-value***
Triglyceride (mg/dl)	434	193.3 ± 69.8	108.1 ± 62.6	**<.001***
HDL (mg/dl)	434	44.1 ± 10.6	62.1 ± 15.3	**<.001***
HbA1c (%)	434	5.4 ± 0.7	5.1 ± 0.3	**.001***
		Carotid intima-media thickness		
		ACHD with MetS (n=62)	**ACHD without MetS (n=372)**	**Mean difference**	**p-value[§]**
Carotid intima-media thickness (mm)	434	0.592 ± 0.087	0.560 ± 0.077	0.032	**.007[§]**

*t-test for unpaired samples between ACHD with MetS and without MetS, [§]general linear model with adjusting for sex and age between ACHD with MetS and without MetS, ACHD: Adults with congenital heart disease, BMI: Body mass index, BP: blood pressure, HDL: high density lipoprotein cholesterol, MetS: metabolic syndrome

6.3 Age-related Cardiovascular Risk in Adult Patients with Congenital Heart Disease

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Individual contribution:

The PhD candidate is the main author of this paper. She sampled the data at the German Heart Center, performed the statistical analysis and the presentation of the results. The manuscript was revised by Priv. Doz. Dr. rer. nat. Jan Müller. The final proof of the manuscript was done by Prof. Renate Oberhoffer, Prof. Hager and Prof. Ewert. The PhD candidate was responsible for the submission process and the implementation of the reviewer's comments into the manuscript in agreement with Priv. Doz. Dr. rer. nat. Jan Müller.

Abstract

Aims: Since the number of adults with congenital heart disease (ACHD) is increasing, age-related cardiovascular diseases become a relevant risk for ACHD. While previous studies investigated isolated risk factors only, this study examines the cardiovascular risk of ACHD based on the PROCAM scores.

Methods and Results: From January 2017 to April 2018, 551 ACHD aged 30 years or older (43.9 ± 9.9 years, 48.3% female) were analyzed for their risk factors of major cardiovascular events within the next ten years using the PROCAM quick check and PROCAM health check. Compared to their individual reference, ACHD had a significantly lower absolute cardiovascular event risk in PROCAM quick check (ACHD: 2.5 ± 4.9%, reference: 3.8 ± 5.2%, $p<.001$) and PROCAM health check (ACHD: 1.8 ± 3.5%, reference: 3.9 ± 5.3%, $p<.001$). The relative risk of ACHD was 37% lower than in the general population calculated with the PROCAM quick test, and 57% lower with the PROCAM health check.

Only 3.4% of the ACHD had a LDL cholesterol higher than 190 mg/dl, 8.3% had a HDL cholesterol lower than 40 mg/dl, and 26.0% had triglyceride higher than 150 mg/dl. Diabetes mellitus was prevalent in 4.0% of the ACHD and 10.9% were current smokers.

Conclusion: According to the PROCAM risk score, ACHD have a lower 10-year risk for major cardiovascular events compared to a healthy reference population. Whether this lower rate of the established risk factors leads to a lower rate of acquired cardiovascular disease has to be clarified in a long-term follow-up.

Keywords: Congenital heart disease, cardiovascular risk, PROCAM score

Introduction

Worldwide the main causes of death in the older population are cardiovascular diseases, and around 80% of all cardiovascular disease related deaths are due to strokes and heart attacks.[139] In adults with congenital heart diseases (ACHD), long-term survival, and thereby a paradigm shift from perioperative to chronic cardiac mortality and non-cardiac death is noticeable.[6, 139] Despite improvements in long-term outcomes, ACHD are rarely cured and many suffer from postoperative residua and sequelae.[15] Following improved long-term outcomes, the age of ACHD increases and therefore, age-related cardiovascular diseases become a relevant risk for these patients.[15, 121, 128]

The development of age-related cardiovascular diseases and atherosclerosis is driven by several risk factors such as diabetes mellitus, body mass index, systolic and diastolic blood pressure, lipid profile, and smoking.[18-21] Some studies in patients with CHD analyzed these single risk factors and suggested increased or abnormal values.[22, 42, 43, 53-57] Increased LDL cholesterol and triglycerides along with lower HDL cholesterol were observed in ACHD [43, 53] as well as a higher prevalence of metabolic syndrome and diabetes mellitus.[22, 42, 43, 54] Furthermore, the incidence of obesity and hypertension is suggested to be higher in patients with CHD than in the reference population.[22, 43]

In contrast, other studies indicate no increased risk or risk factors in ACHD compared to the general population.[56, 57] Overweight and obesity was less common in male ACHD than in the reference population [56], lipid profiles unobtrusive [53, 140] and prevalence of coronary artery disease similar as in the general population.[57]

Taking the variety of single risk factors of cardiovascular diseases in ACHD into account, the aim of this study was to examine the 10-year risk of a major cardiovascular event within the next ten years based on multiple risk factors in one score. Therefore, the PROCAM score, a score based on German reference values, was calculated for ACHD using multiple risk factors and then compared to the German reference.

Patients and Methods

Study subjects

In total, 551 ACHD aged 30 years and older (43.9 ± 9.9 years, 48.3% female) with various types of CHD were prospectively recruited during their routine follow-up appointment at the German Heart Centre in Munich from the outpatient department between January 2017 and April 2018. Blood samples were available for 445 ACHD. All patients were analyzed for established risk factors to face a major cardiovascular event within the next ten years.

Based on the underlying diagnosis, the ACHD were grouped into 11 subgroups: 'aortic stenosis', 'coarctation of the aorta', cyanotic patients which are native or palliated, 'Ebstein anomaly', 'Fontan circulation', 'isolated shunts' including atrial, ventricular, and atrioventricular septal defect, 'pulmonary stenosis', 'Tetralogy of Fallot', 'Transposition of the Great Arteries after Rastelli repair' including congenital corrected Transposition of the Great Arteries, 'Transposition of the Great Arteries after Senning or Mustard', and others.

All patients gave written informed consent and the study was approved by the local ethical board of the Technical University of Munich (project number: 64/17S) and is part of the CARING (Cardiovascular Risk in grown-up congenital heart disease) project.

Prospective Cardiovascular Münster (PROCAM) study

The 10-year risk of a major cardiovascular event, which means fatal or non-fatal myocardial infarction or stroke, was calculated and classified with the PROCAM (Prospective Cardiovascular Münster) study score. The PROCAM score is comparable to the Framingham risk score [50] but based on a German cohort of 18,460 men and 8,518 women 20-78 years at study entry and followed for an average of 11.7 years.[49] The 10-year risk of a major cardiovascular event was calculated with two scores of the PROCAM study: the PROCAM quick check and the PROCAM health check. The PROCAM quick check includes the factors age, sex,

height, weight, systolic blood pressure, diabetes (yes/no), current smoking status (yes/no), antihypertensive drug treatment, and family history of a cardiovascular event.

In the PROCAM health check, height, weight, and antihypertensive drug treatment status is substituted with LDL cholesterol, HDL cholesterol, and triglyceride.

For further information and online calculations, follow this link: http://cmd-taskforce.org/risk-assessment/.

The factors smoking status (currently: yes/no), hypertensive drug treatment (currently: yes/no), and the presence of a cardiovascular event of a first-degree family member before the age of 60 (yes/no) were asked in a questionnaire. Blood pressure measurement was conducted in all ACHD patients with the oscillometric measurement device Mobil-o-Graph (I.E.M, Stolberg, Germany). After resting in supine position for five minutes, the measurement was performed on the left upper arm with an arm-adjusted cuff size. Blood sampling was performed in non-fasting state and sitting position.

Blood samples were categorized according to the European Guidelines.[67, 68] Elevated LDL cholesterol was defined at >190 mg/dl, low HDL cholesterol was defined at <40 mg/dl, elevated triglycerides were defined at >150 mg/dl, and an $HbA1_c$ higher than 6.5% was defined as the existence of diabetes mellitus type 2.

Physical Activity Assessment

Physical activity was assessed based on the single question: “On how many days of a regular week are you active for at least 30 minutes? That includes sport activities but also contains forms of regular activities such as brisk walking and cycling long enough to get your heart pumping or become short of breath?”. Patients with a response of five or more days met the WHO criteria of 150 minutes physical activity per week [141] and were categorized as “active”.

Data analyses

Descriptive data of all ACHD is expressed in mean values and standard deviations. The PROCAM study provides a mean sex- and age-adjusted risk for the PROCAM quick check and the PROCAM health check. Using these sex- and age-based reference values, t-tests for paired samples were calculated to analyze the cardiovascular risk of ACHD. In addition, sex differences for the single risk factors were calculated with a t-test for unpaired samples or a chi-square test (chi-square test for the factors diabetes mellitus, hypertensive drug treatment, positive family history, current smoking status). Furthermore, a t-test for unpaired samples was performed for differences between active and non-active ACHD for the PROCAM quick check and the PROCAM health check.

All tests were performed using SPSS (version 23.0, IBM Corporation). The level of significance for all tests was set to $<.05$. Figures were created with R Studio (version 1.1.423).

Results

ACHD had a significantly lower absolute 10-year risk of a major cardiovascular event in the PROCAM quick check (ACHD: 2.5 ± 4.9%, reference: 3.8 ± 5.2%, p<.001) and the PROCAM health check (ACHD: 1.8 ± 3.5%, reference: 3.9 ± 5.3%, p<.001) compared to the general population (Table 1, Figure 1 and 2). The relative risk of ACHD was 37% lower than in the general population calculated with the PROCAM quick check, and 57% lower calculated with the PROCAM health check.

In total, 3.4% of the ACHD had increased LDL cholesterol higher than 190 mg/dl, 8.3% of the ACDH had reduced HDL cholesterol lower than 40 mg/dl, and 26.0% had triglyceride higher than 150 mg/dl. In addition, 35.5% were overweight and 13.5% obese. Increased systolic blood pressure higher than 140 mmHg was present in 11.1% and increased diastolic blood pressure higher than 90 mmHg was present in 9.6%. Diabetes mellitus was prevalent in 4.0% of the included ACHD. Another 10.9% were current smokers (Table 1 and Figure 3). Differences within the particular CHD subgroups are provided in Table 2.

Moderate-to-vigorous physical activity of at least 30 minuntes on five or more days a week were reported by 296 (56.5%) patients. There were no differences when comparing active and inactive patients for the PROCAM quick check (active: 2.2 ± 3.6% vs. inactive: 2.6 ± 5.3%, p=.256) and PROCAM health check (active: 1.6 ± 3.0% vs. inactive: 1.9 ± 3.7%, p=.501).

Female and male ACHD differed significantly in most of the measured risk factors, as well as in both PROCAM risk calculations (Table 1).

Discussion

In ACHD risk calculations based on a healthy reference population revealed a lower 10-year risk of a major cardiovascular event compared to the general population. Including blood parameters in the PROCAM health check, the risk of ACHD is calculated to be only half as high as the risk in the general population.

10-year risk for cardiovascular events

Only one study has analyzed the total risk of a cardiovascular event among ACDH so far.[53] Lui and colleagues [53] showed in their study on 103 patients that the predicted risk for atherosclerotic cardiovascular disease in ACHD for the following ten years resulted in a relatively low risk. 90% of the patients had a 10-year cardiovascular event risk below 10% calculated with three different risk scores (atherosclerotic cardiovascular disease risk survey, Framingham Study, and Reynolds). Our findings are in line with these results as ACHD have a significantly lower rate of risk factors as well as lower PROCAM scores when compared to the general population.

However, analyzing previous studies, a higher risk of cardiovascular events would be expected, as various single risk factors are increased.[22, 42, 43, 53-57] For example, Moons and colleagues showed in a retrospective analysis of 1,976 ACHD that only 20.4% of the male and 21.0% of the female ACHD showed no cardiovascular risk factor.[22] Also Lui et al. [53] showed that 70% of the patients with moderate or great complexity of CHD are exposed to at least one risk factor for atherosclerotic cardiovascular disease. However, both studies did not discuss that atherosclerotic risk factors are also a big concern and of high prevalence in the general population.[142] It is therefore questionable to conclude that abnormalities in single risk factors automatically yield to a higher overall risk for a cardiovascular event.

Single Risk factors

Diabetes mellitus

Altered insulin sensitivity and disordered glucose metabolism in ACHD resulting in diabetes are reported in many studies. [22, 43, 54, 140, 143] In line with this research, our study also showed that the prevalence of diabetes mellitus in ACHD was 4.0%, whereas only 3.2% in the German population aged 40 to 49 years old.[144] The mechanisms how genetics and environmental risk factors act together are not fully explored. However, animal models and human studies showed that hypoxia has negative effects on glucose metabolism.[54] Therefore, further research has to address how cyanosis in infancy or reduced oxygen saturation in ACHD (e.g. in Eisenmenger patients) may expose those patients to higher risk for diabetes.

Smoking

Smoking is a major cause for cardiovascular disease due to various reasons such as increased platelet aggregability, reduced HDL cholesterol, and arboxy-hemo-globinemia.[145] In our cohort of ACHD only 10.9% were smokers which is much less than in the German population with 29.7%.[146] Other studies also suggest that this major risk factor is well controlled in ACHD as prevalence is estimated at 13.5% in the Netherlands [147], 17.5% in Belgium [22], 19.4% in the UK [143], and only 2% in the US [53]. The latter might also explain the low 10-year risk of a major cardiovascular event in this study because “smoking”, the biggest contributor in risk score estimates, is minor.

This also supports our understanding to focus not only on single risk factors, since the cardiovascular burden of smoking is more serious than slight overweight or marginal increased lipid profiles. Definitely, all of these are cardiovascular risk factors but they contribute different to the overall risk stratification, and the low prevalence of smoking could help to explain the overall lower 10-year risk in our study.

Dyslipidemia

Findings on dyslipidemia or lipid levels in general are underexplored and controversial. In a German-wide study 11.4% of the healthy adults had a reduced HDL cholesterol in comparison to only 8.3% of the ACHD in this study.[148] Moreover, only 3.4% of our ACHD had increased LDL cholesterol levels and 26.0% increased triglycerides. Lower LDL cholesterol levels in ACHD were also seen in other studies [53, 140] whereas, triglycerides remained similar compared to a reference cohort.[140] HDL cholesterol was decreased in 28% [53] or significantly lower compared to a German reference cohort.[140] From the variety of the studies on lipids it remains questionable that there is an environmental or genetically determined risk in patients with CHD. In cyanotic CHD it is quite the contrary, where persistent hypoxia may trigger secondary erythrocytosis, hyperbilirubinemia, lower cholesterol levels, and atherosclerotic risk.[149]

Hypertension

Compared to the German reference [150], our ACHD have a lower systolic (ACHD: 121 mmHg vs. reference: 126 mmHg) and a slightly lower diastolic blood pressure (ACHD: 75 mmHg vs. reference: 78 mmHg). In contrast, other studies found a higher prevalence of hypertension in ACHD.[22, 43] Besides, in several ACHD subgroups higher arterial stiffness (the ability of the vessels to dilate and recoil) was found.[151] The lower blood pressure seems to be a result of an extensive hypertensive therapy that 42% of our patients followed. However, it should not have confounding effects on the PROCAM 10-year risk calculation since blood pressure and hypertensive medication were part of the variables.

Overweight and Obesity

The prevalence of overweight in the present study is similar to the German reference values in female ACHD (ACHD: 28.7%, reference: 27.8%), but lower in male ACHD (ACHD: 41.9%, reference: 47.1%). In general, obesity is less prevalent in female and male ACHD compared to the German reference (female

ACHD: 9.8%, reference: 18.6%; male ACHD: 16.9%, reference: 22.9%). In male ACHD, lower prevalence of overweight and obesity was also found in Sandberg et al. [56] and also Zomer and colleagues reported less obesity in all ACHD.[152] In the most recent study from the UK, 42.8% of the 3069 patients were overweight. However, it is worth to mention that patients with higher BMI had a lower mortality, especially in symptomatic patients with complex cardiac defects.[153] In the literature this phenomenon is known as obesity paradox and crucial for patients with CHD because fast cardiac cachexia can occur due to heart surgeries or cardiac decompensations. So overweight might be a risk factor for atherosclerosis driven cardiac event in the general population, whereas ACHD may profit from slight overweight in terms of life expectancy.

Physical Activity

Most of our ACHD cohort (56.5%) reported five or more days of physical activity and met the WHO recommendation of 150 minutes physical activity per week, which is above the German average of 39%.[154] This confirms objective measures from our institution.[155] A physically active lifestyle is an important issue of all the medical staff at the German Heart Centre in Munich and a cornerstone of our aftercare. So, it cannot be ruled out that the beneficial risk factor profile in regards to physical activity is a result of recommendations for active behavior at our institution.

Clinical Relevance

Coronary artery disease is rare and not more frequent in ACHD compared to healthy controls.[57] Especially cyanotic ACHD seems to be on a lower risk for atherosclerotic cardiovascular events.[156] These findings are confirmed as vascular issues contributed only to either 12.2% or 14.3% of all deaths in two national registries, and patients with CHD died from other non-cardiovascular reasons such as progressive heart failure or sudden cardiac death.[157]

Furthermore, it is questionable if the risk factors included to the PROCAM scores cover the actual risk of a cardiovascular event in ACHD. It is unknown whether and to what extent congenital lesions leave coronary arteries more vulnerable to premature coronary artery disease, especially in patients with anatomical abnormalities of the coronary arteries, coronary arteries that were manipulated as part of the surgical repair, and conditions associated with widespread vasculopathy.[158] Likewise, it is not clear how premature stiffening of the arterial vessels contributes to heart failure and atherosclerosis in this patient population.[151]

Nevertheless, it is important to control the risk factors included to the PROCAM scores in ACHD by the medical staff in tertiary centers to minimize the risk of a cardiovascular event based on these risk factors.

Conclusion

ACHD have lower risk factor profile for a major cardiovascular event within the next ten years compared to the German reference. In addition to the risk factors included in the PROCAM score, ACHD seem to have a healthier lifestyle. Whether the reduced risk calculated from the PROCAM scores really translates to a reduced risk for acquired cardiovascular events in patients with CHD, has to be confirmed in the long-term follow-up of this cohort.

Limitations

The German Heart Centre in Munich is a specialized center for CHD and the majority of ACHD have defects of severe complexity. This might bias the results, as it does not show the real distribution of CHD severity in the usual population of ACHD. Furthermore, all ACHD from our institution are encouraged to adopt a healthy and active lifestyle and could therefore represent a healthier subgroup.
The PROCAM score covers a broad age range which makes the results also more robust in younger age groups. However, it was built from the general German population and it is not clear that the estimates could be adapted for patients with CHD. The PRCOCAM scores should further be calculated before lipid-lowering drugs are prescribed which was not possible in our context. However, only 2.5% took lipid-lowering drugs and thus the impact can probably be neglected.
Additional risk factors contributing to cardiovascular events in ACHD are not identified so far and long-term outcomes are needed to validate the predictive value of PROCAM and other scores in ACHD.

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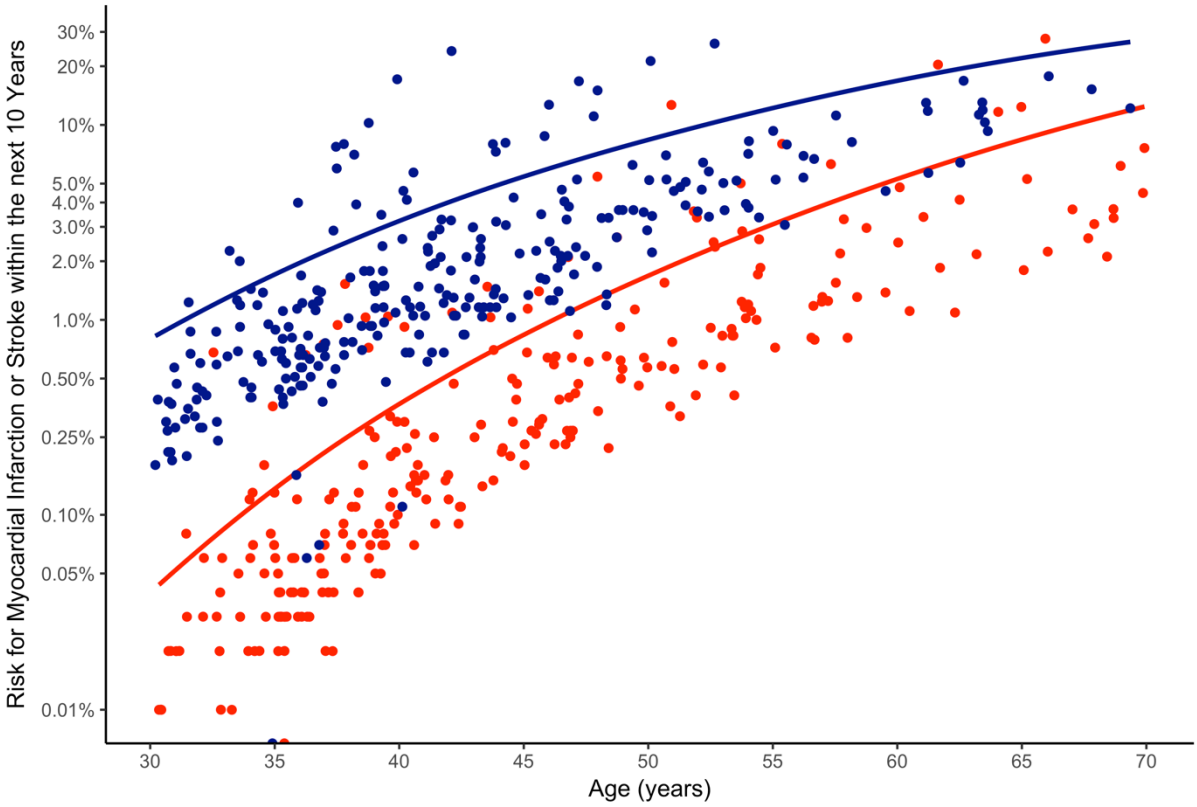
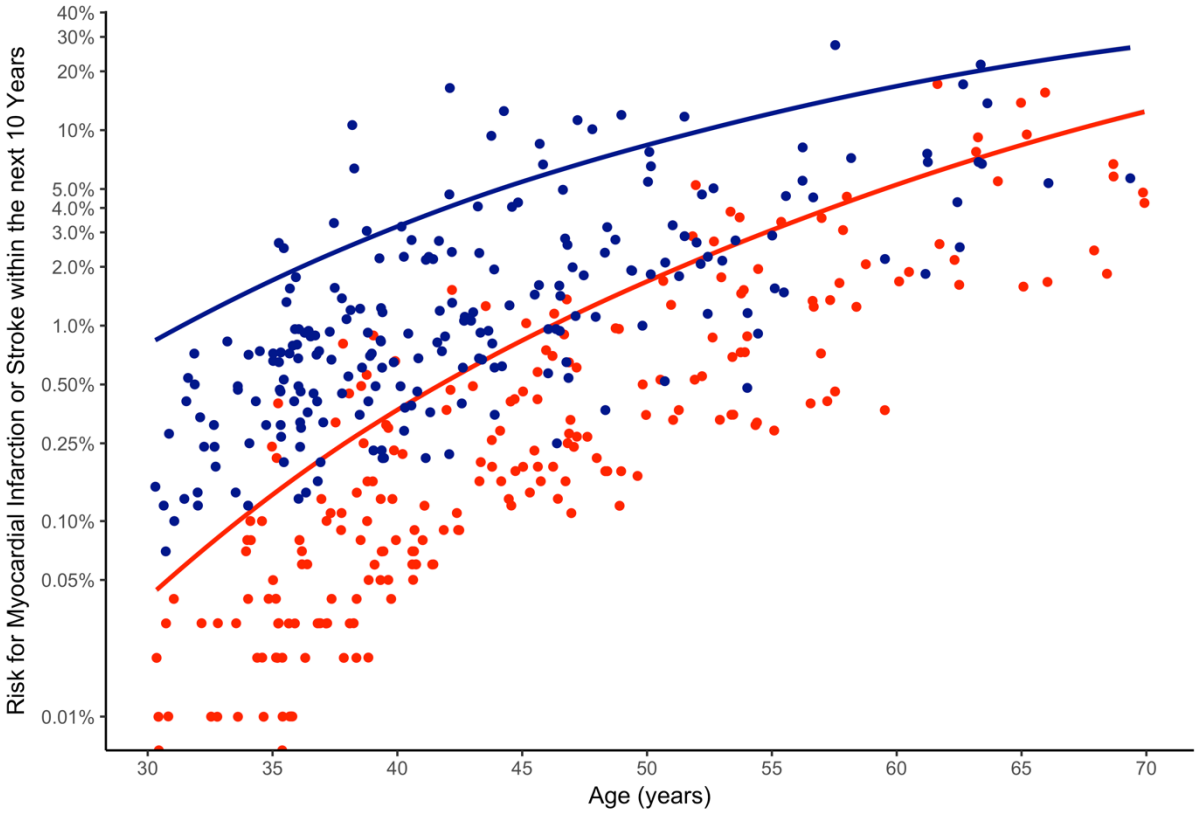
Figures

Figure 1: PROCAM quick check in female and male ACHD and the age-related reference



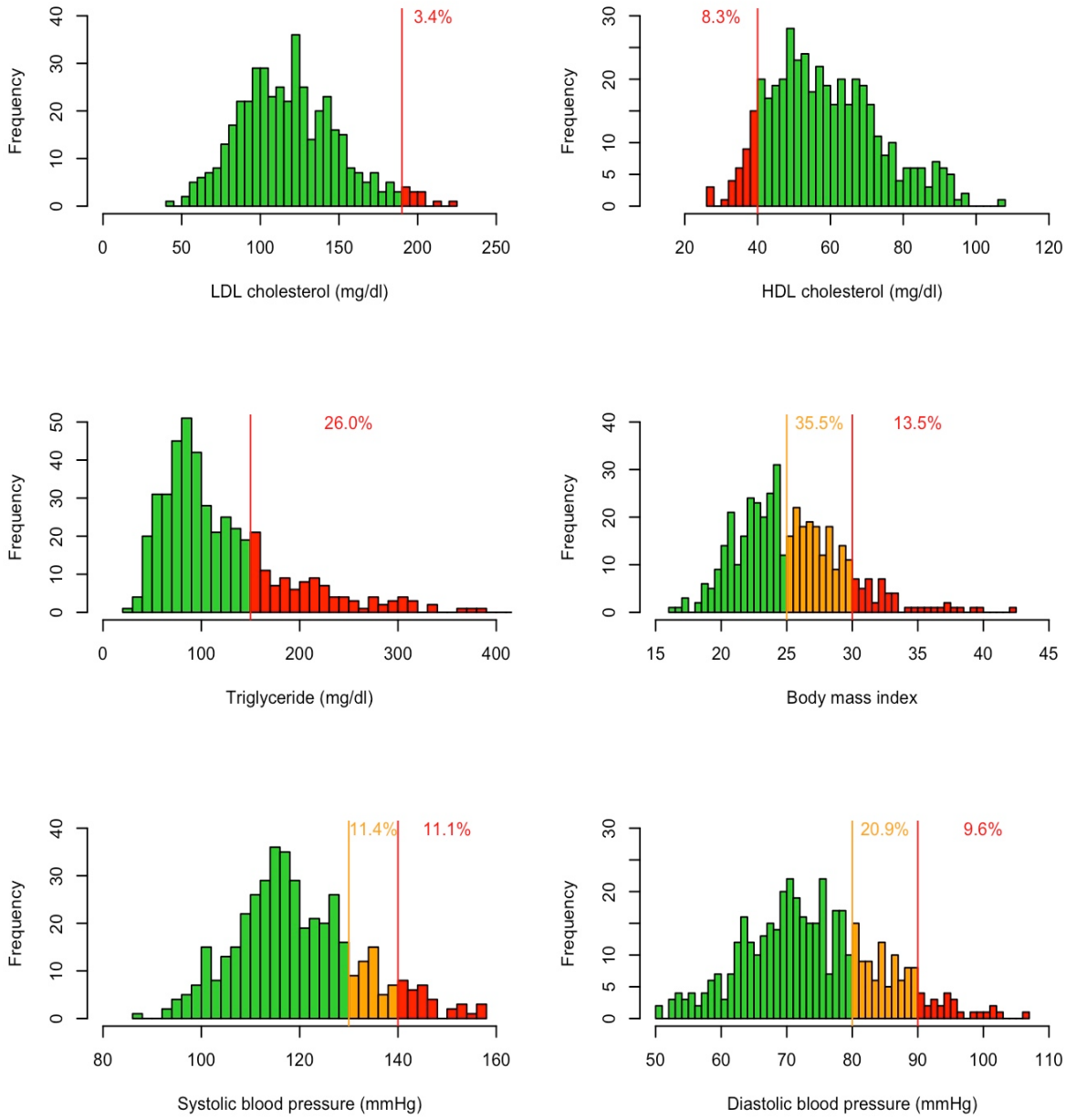
Blue dots: male adults with congenital heart disease, blue line: male reference, red dots: female adults with congenital heart disease, red line: female reference, ACHD: Adults with congenital heart disease

Figure 2: PROCAM health check in female and male ACHD and the age-related reference



Blue dots: male adults with congenital heart disease, blue line: male reference, red dots: female adults with congenital heart disease, red line: female reference, ACHD: Adults with congenital heart disease

Figure 3: Distribution of the single risk factors in all ACHD



LDL: low density lipoprotein, HDL: high density lipoprotein

Table

Table 1: Cardiovascular risk factors of all ACHD and differences between female and male ACHD

				Anthropometric data		
	n	**All ACHD**		**Female ACHD (n=266)**	**Male ACHD (n=285)**	**p-value***
Age (years)	551	43.9 ±9.9		45.1 ± 10.3	42.9 ± 9.4	**.008***
BMI	549	25.5 ± 4.3		24.6 ± 4.4	26.3 ± 4.1	**<.001***
Hip-to-waist-ratio	495	0.86 ±0.09		0.80 ± 0.07	0.91 ± 0.07	**<.001***
Systolic BP (mmHg)	551	121.3 ±14.9		119.0 ± 14.8	123.5 ± 14.8	**<.001***
Diastolic BP (mmHg)	551	74.7 ±11.3		72.3 ± 10.3	77.0 ± 11.8	**<.001***
				Blood lipids		
		All ACHD		**Female ACHD (n=195)**	**Male ACHD (n=204)**	**p-value***
LDL cholesterol (mg/dl)	445	118.9 ±32.6		111.7 ± 30.5	121.7 ± 34.5	.070*
Triglyceride (mg/dl)	454	123.3 ±71.6		111.7 ± 60.5	134.6 ± 79.6	**.001***
HDL cholesterol (mg/dl)	446	59.0 ±16.2		64.5 ± 16.6	53.6 ± 13.8	**<.001***
HbA1c (%)	415	5.2 ±0.4		5.1 ± 0.4	5.2 ± 0.5	.618*
				Risk factors		
		All ACHD		**Female ACHD (n=239)**	**Male ACHD (n=266)**	**p-value§**
Diabetes mellitus (%)	551	4.0		3.0	4.9	.254§
Hypertensive agents (%)	551	41.7		38.0	45.3	.083§
Positive family history (%)	551	14.0		14.7	13.3	.653§
Current smoker (%)	551	10.9		9.4	12.3	.530§
				Risk Scores		
		All ACHD	**Reference**	**p-value°**	**Female ACHD (n=239)**	**Male ACHD (n=266)**	**p-value***
PROCAM quick check	551	2.5 ±4.9	3.8 ±5.2	**<.001°**	1.3 ± 3.4	3.6 ± 5.7	**<.001***
PROCAM health check	445	1.8 ±3.5	3.9 ±5.3	**<.001°**	1.1 ± 2.8	2.5 ± 4.0	**<.001***

°t-test for paired samples for the PROCAM scores between patients and reference, *t-test for unpaired samples between female and male adults with congenital heart disease, §chi-square test between female and male adults with congenital heart disease, ACHD: Adults with congenital heart disease, BMI: Body mass index, BP: blood pressure, LDL: low density lipoprotein, HDL: high density lipoprotein

7 Discussion

The purpose of this PhD thesis was to quantify the actual age-related cardiovascular risk in patients with CHD compared to the general population. It has been shown that arterial stiffness is increased in most of the diagnostic subgroups in children with CHD compared to healthy peers. Furthermore, ACHD with MetS are affected by a thicker cIMT than ACHD without MetS. Thus, both groups – children with CHD and ACHD with MetS – show increased cardiovascular risk factors. However, in contrast and according to the PROCAM, ACHD have a lower risk of a major cardiovascular event within the next 10 years compared to the German reference cohort.
Based on these three analyses, the research question of this thesis cannot be answered clearly at first glance and has to be discussed in detail.

Looking more closely at the individual studies of this PhD thesis and their methods, one finds reasons why their results are not identical. The paper 'Increased arterial stiffness in children with congenital heart disease' used the Mobil-o-Graph device of I.E.M, which is validated by several studies with healthy individuals.[78, 79] However, the device has not been validated for children with CHD so far, leading to the question whether the central blood pressure values calculated by an algorithm of the device are reliable for individuals with CHD. It is also possible that artificial materials like patches, sutures, and scars in the heart alter the pressure wave, mimicking higher arterial stiffness.
The device uses, among other parameters, an average distance between cuff and aorta for the calculation. For this calculation method to be valid for children with CHD, it is a prerequisite that the average distance between cuff and aorta is applicable for these children. Compared to healthy counterparts, it must be assumed that this distance is different among children with CHD due to the altered anatomy or surgical interventions. Examples include individuals with CoA (surgical correction: End-to-end anastomosis of the aorta leading to shorter dis-

tance) and patients with TGA (surgical correction: arterial switch operation leading to a sharper angle). Certainly, there are also anatomical variations in healthy children but the algorithm of the Mobil-o-Graph nevertheless generates valid results, as validation studies proved.[78, 79] In addition, the results of the paper 'Increased arterial stiffness in children with congenital heart disease' about significantly stiffer vessels in children with left heart obstructions including individuals with CoA, children with TGA and univentricular hearts after total cavopulmonary connection (TCPC) are in line with comparable studies applying other methods.[30, 31, 79, 87, 97, 102, 105, 110, 111, 115, 116]

For example, in children with CoA an increased stiffness of the pre-stenotic region was found and this stiffness was still prevalent even after surgery, suggesting a genetic component.[106, 107] Voges et al. assumed that patients with TGA after arterial switch operation have impeded aortic distensibility by fibrosis around the transposed arteries or the pulmonary artery branches embracing the aorta after Lecompte maneuver.[102] Furthermore, an early pulse wave reflection was associated with a post-surgical sharper angulation of the neo-aorta and aortic arch.[111, 112] The same results were found in children with hypoplastic left heart syndrome where the aortic arch reconstruction with patches indicated to result in increased stiffness of the ascending aorta.[117]

Therefore, the central blood pressure values obtained from the Mobil-o-Graph can be accepted as valid in our context. Increased arterial stiffness in children with CHD predisposes these individuals for premature cardiac damage and vascular remodeling. Consequences include arterial hypertension and increased afterload, leading to tremendous burden for the systemic ventricle. However, being exposed to one risk factor of a cardiovascular event in early childhood does not automatically result in an increased age-related cardiovascular risk. As previously mentioned, the general population has cardiovascular risk factors that persist from childhood to adulthood,[35, 36] but this fact is unclear in children with CHD. Therefore, close monitoring of these children is necessary in order to

evaluate if these risk factors persist until adulthood. There is reason to fear that if these risk factors persist, the age-related cardiovascular risk is even higher.

The second paper ‘Metabolic syndrome in adult patients with congenital heart disease is associated with increased carotid intima-media thickness’ is based on two parameters: cIMT and MetS.

A point of criticism in measuring cIMT is that an increased cIMT does not predict cardiovascular events directly, as big cohort studies question the merit of cIMT progression and its effect on cardiovascular risk in the general population.[126, 138]

On the other hand, the Framingham Risk Score for 10-year risk prediction of first-time myocardial infarction or stroke was improved slightly by adding cIMT measurements. Thus, cIMT is therefore still a well-accepted parameter for cardiovascular morbidity and mortality.[126]

A further possible bias is the interrater variability when analyzing the cIMT by ultrasound. To minimize this impact, all examiners were instructed by the same sonographer. The large sample size is another way to minimize the interrater variability. In addition, the impact of the interrater variability is present in ACHD with MetS and without MetS as the MetS classification was done retrospectively. Therefore, it is to be assumed that this bias can be neglected.

The results of this paper also depend on the definition criteria of the MetS. Many patients with ACHD were prescribed ACE inhibitors, diuretics or beta-blockers for other reasons than hypertension. Since one criteria of the MetS definition is hypertensive therapy, the risk factor “blood pressure”, and MetS in general could have been overestimated. However, in the definition of MetS there is no possibility to consider that fact.

Furthermore, it is questionable whether the criteria of MetS can be compared directly between the normal population and ACHD patients. So far, the criteria of MetS were not evaluated prospectively in ACHD with regard to mortality and morbidity leading to the following questions:

- Does the combination of criteria have the same consequences in ACHD and the normal population?
- Are new cut-offs and guidelines needed for ACHD?
- Is the weighting of the criteria in ACHD and the population the same, or should a high blood pressure have a higher weight in ACHD due to higher afterload for an already diseased heart?

In addition, depending on eight different MetS definitions, Reinehr and colleagues reported a varying prevalence of MetS ranging from 6-39%.[133] Due to this wide range,[133] using another definition of MetS could have a major impact on the results of this study. The potential deviation could result in a higher significant difference or no significant difference between ACHD with MetS and ACHD without MetS. However, the study of Deen and colleagues [42] demonstrated a similar prevalence of MetS in ACHD patients, as our results did (Deen: 15% vs. Häcker: 14.3%), making the classification with the used definition of MetS for ACHD realistic.
In conclusion, the results of the second paper 'Metabolic Syndrome in Adult Patients with Congenital Heart Disease is Associated with Increased Carotid Intima-Media Thickness' can also be accepted as valid as only ACHDs were compared with each other. Regardless of the weighting, the risk factors are also harmful for ACHD due to alterations in the vascular structure (significant thicker cIMT) in ACHD with MetS.

The raised questions of the MetS, especially the weighting, are also applicable for the PROCAM score, the method of the last paper 'Age-related Cardiovascular Risk in Adult Patients with Congenital Heart Disease'. The following figure shows the underlying components and the weighting for each parameter within the PROCAM score.

LDL* cholesterol ($mg\ dL^{-1}$)		HDL† cholesterol ($mg\ dL^{-1}$)		Systolic blood pressure (mmHg)		Smoking status	
≤ 100	0	≤ 35	11	< 110	0	No	0
101–105	1	36–37	10	110–119	1	Yes	12
106–110	2	38–39	9	120–129	2		
111–115	3	40–41	8	130–139	3	Family history	
116–120	4	42–43	7	140–149	4		
121–125	5	44–45	6	150–159	5	No	0
126–130	6	46–47	5	160–169	6	Yes	5
131–135	7	48–49	4	170–179	7		
136–140	8	50–51	3	≥ 180	8		
141–145	9	52–53	2				
146–150	10	54–55	1	Fasting blood glucose ≥ 120 $mg\ dL^{-1}$ or diagnosis of diabetes mellitus			
151–155	11	> 55	0				
156–160	12						
161–165	13	Triglycerides ($mg\ dL^{-1}$)					
166–170	14	< 100	0	No	0		
171–175	15	100–149	2	Yes (men)	9		
176–180	16	150–199	3	Yes (women)	11		
181–185	17	≥ 200	4				
186–190	18						
191–195	19						
≥ 196	20						

*Low-density lipoprotein, †high-density lipoprotein.

Figure 8: Parameters of the PROCAM score and their weight for the risk calculation of a major cardiovascular event[159]

So far, there are no studies for ACHD showing the severity of the different risk factors used in the PROCAM score concerning a major cardiovascular event. However, the study of Bokman and colleagues[160] indicated that the weighting factors may be different in ACHD by showing that the traditional risk factors such as hypertension, hypercholesterolemia, and smoking were only associated with coronary artery disease but not with strokes. Thus, the conclusion can be drawn that not all risk factors have the same consequence for ACHD and the healthy reference population.

The PROCAM score has further deficiencies. HDL cholesterol values in the PROCAM score calculation are capped at 55 mg/dl (cf. Figure 5 in *Discussion*), classifying all higher values as neutral for the risk calculation. However, according to a recent study, HDL cholesterol and mortality are not associated linearly but demonstrated a U-shaped association with the lowest risk in the middle and an increased risk at the low and high ends of HDL cholesterol.[161] However, with a mean HDL cholestrol value in ACHD with 59.0 ± 16.3 mg/dl, the impact is probably negligible.

In addition, the PROCAM score does not take into account whether the patient takes lipid-lowering drugs, and the intake of hypertensive agents is considered only in the PROCAM quick check. Does that mean that a patient with lipid-lowering or blood pressure-lowering agents is as healthy as a patient with natural low values? What about side effects of the drugs? However, only 2.5% took lipid-lowering drugs and thus the impact can probably also be ignored. Nevertheless, 41.7% of all ACHD took hypertensive agents and it remains unclear how many patients were prescribed hypertensive agents for reasons other than hypertension, such as reducing pre- or afterload, or to reduce arrhythmia. Since only one PROCAM score calculation takes the intake of hypertensive agents into account, but both showed the same trends of results, this point of deficiency might not be that relevant either.

The impact of smoking is assessed in a binary way: currently smoker or non-smoker. But no further details are considered, such as the duration of tobacco consumption, how many cigarettes per day/week or how long the patients have been abstinent from tobacco. However, recent studies showed that the duration and the amount of tobacco consumption have an impact on the risk of cardiovascular disease and cardiovascular health.[162, 163] Furthermore, if the package per year is equal, smoking for a longer duration less cigarettes per day was more noxious than smoking for a shorter duration but more cigarettes per day,[163] meaning that the PROCAM score misses important information.

The PROCAM score takes the family background into account since the genes have a great influence on the development of cardiovascular diseases.[25] What if ACHD with a familiar predisposition are already dead and this study represents a positively skewed sample? As the mean age of 43.9 ± 9.9 years is relatively high for ACHD, it could be that predominantly patients without familiar predisposition are part of this study.

Furthermore, some studies indicated that the predictive power for cardiovascular events of other scores is higher than in the PROCAM score.[50, 164] All criticism

aside, a recent study by Chrubasik and colleagues[165] has confirmed the PROCAM score's weighting of blood pressure. And at the end, the German reference cohort was the decisive factor to use the PROCAM score for this work. In addition, PROCAM score has with almost 27,000 reference persons between 20 and 78 years old, whom were followed for an average of 11.7 years, [49] a very solid data base. It is therefore a very helpful instrument for a quick first risk assessment of a major cardiovascular event, even if this means an equation of ACHD and the healthy population.

In conclusion, the lower risk of a major cardiovascular event within the next 10 years compared the German reference of the PROCAM score is reasonable because the included risk factors are checked regularly during routine check-ups and countermeasures are initiated. Thus, the prevalence of increased risk factors is lower in ACHD compared to the German reference.

However, several studies demonstrated a higher risk of strokes in ACHD than in the reference population[122, 166] and in adult individuals with simple CHD, myocardial infarction is the main cause of death,[167, 168] so that major doubts are arising whether the PROCAM score is valid for ACHD.

8 Conclusion

The purpose of this study to quantify the actual age-related cardiovascular risk in patients with CHD compared to the general population is not trivial, even after the discussion with review of the methods.

In conclusion, the single risk factors for a major cardiovascular event have to be kept at a minimum and regularly controlled in individuals with CHD, in order to limit the risk of cardiovascular events and diseases. Since ACHD usually died in younger ages in the past, the analysed risk factors were not relevant so far, due to low exposure time. But future studies have to further evaluate the single components in terms of their effect on mortality and morbidity for individuals with CHD.

Using the established PROCAM score seems unlikely to calculate the real risk of a major cardiovascular event in ACHD definitively and future studies have to analyze the actual eligibility. Therefore, it is highly recommended to re-examine the ACHD patients included in this work after 10 years for a long-term follow-up, in order to evaluate their actual health status. Depending on the results of the future studies, the existing PROCAM score could be optimized and calibrated for ACHD, or a completely new score could be developed. But already on the basis of this study, an adjustment of the weighting and new parameters within the PROCAM score seems to be needed. First suggestions include a non-linear assessment of blood pressure as well as the consideration of septal defects, previous shunts, and mechanical valves, as shown by a factor analysis for stroke and coronary artery disease of Bokman and colleagues.[160]

However, independent of the score discussion, patients and their medical doctors have to prepare for the continuously increasing life expectancy and the associated age-related cardiovascular diseases. As an outcome of this study, it is recommended that ACHD have their cardiovascular risk factors checked regularly in order to prevent major cardiovascular events such as strokes and myocardial infarctions.

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10 Appendix

Appendix A

Zustimmungserklärung zur Studie (für Kinder von 6-17 Jahren)

„Kardiovaskuläres und sportmotorisches Screening zur Gesundheitsprävention bei Jugendlichen und Heranwachsenden mit angeborenem Herzfehler“

Für

Kind/Jugendlicher: _____
(Vorname Nachname; bitte in Druckbuchstaben schreiben)

Geburtsdatum: _____ (TT.MM.JJJJ)

Ich erkläre mich damit einverstanden, an der Studie „Kardiovaskuläres und sportmotorisches Screening zur Gesundheitsprävention bei Jugendlichen und Heranwachsenden mit angeborenem Herzfehler“ teilzunehmen. Ich bin damit einverstanden, dass die beschriebenen Untersuchungen durchgeführt werden.

Ich bin damit einverstanden, dass die im Rahmen der Untersuchung erhobenen Daten aufgezeichnet, ausgewertet und gespeichert werden. Ich bin darüber informiert worden, dass die Speicherung und Verarbeitung der erhaltenen Daten den Bestimmungen des Datenschutzgesetzes unterliegen.

Ich weiß, dass ich jederzeit ohne Nachteile und ohne Angabe von Gründen mit sofortiger Wirkung diese Zustimmung zurückziehen und die gespeicherten Daten löschen lassen kann.

Ich wurde über das Ziel und den Zweck dieser klinischen Studie und die praktische Durchführung aufgeklärt. Beiliegende Information habe ich erhalten, gelesen und verstanden. Eine Kopie dieser Einverständniserklärung haben ich ebenfalls erhalten.

Ort/Datum: _____

_____ _____

Unterschrift des Kindes (Probanden) ***Unterschrift der Studienleitung***

Appendix B

Einverständniserklärung zur Studie (für Eltern)

„Kardiovaskuläres und sportmotorisches Screening zur Gesundheitsprävention bei Jugendlichen und Heranwachsenden mit angeborenem Herzfehler“

Für

Kind/Jugendlicher: _____
(Vorname Nachname; bitte in Druckbuchstaben schreiben)

Geburtsdatum: _____ (TT.MM.JJJJ)

Ich erklären mich damit einverstanden, dass mein Kind an der Studie „Kardiovaskuläres und sportmotorisches Screening zur Gesundheitsprävention bei Jugendlichen und Heranwachsenden mit angeborenem Herzfehler“ teilnimmt. Ich bin damit einverstanden, dass die beschriebenen Untersuchungen durchgeführt werden.

Ich bin damit einverstanden, dass die im Rahmen der Untersuchung an meinem Kind erhobenen Daten anonymisiert aufgezeichnet, wissenschaftlich ausgewertet und archiviert werden. Ich stimme ihrer Veröffentlichung unter der Voraussetzung zu, dass jeder Bezug zu meinem Kind unkenntlich gemacht wurde. Ich bin darüber informiert worden, dass die Speicherung und Verarbeitung der erhaltenen Daten den Bestimmungen des Datenschutzgesetzes unterliegen.

Ich weiß, dass ich jederzeit ohne Nachteile und ohne Angabe von Gründen mit sofortiger Wirkung dieses Einverständnis zurückziehen und die gespeicherten Daten löschen lassen kann.

Ich und mein Kind wurden über das Ziel und den Zweck dieser klinischen Studie und die praktische Durchführung aufgeklärt. Beiliegende Probandeninformation haben ich erhalten, gelesen und verstanden. Eine Kopie dieser Einverständniserklärung haben wir ebenfalls erhalten.

Ort/Datum: _____

_____ _____

Unterschrift des Erziehungsberechtigten ***Unterschrift der Studienleitung***

Ich erkläre hiermit verpflichtend, dass der Vater/die Mutter (also der Erziehungsberechtigte, der nicht unterschrieben hat) mit der Teilnahme an der Studie einverstanden ist.

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Appendix C

Klinik für Kinderkardiologie und angeborene Herzfehler

Direktor: Prof. Dr. med. P. Ewert

Deutsches Herzzentrum München
des Freistaates Bayern
- Klinik an der Technischen Universität München -

EINVERSTÄNDNISERKLÄRUNG

zur Studie

Quantifizierung des kardiovaskulären Risikos bei Erwachsenen mit angeborenem Herzfehler

Ich wurde über das Ziel und den Zweck dieser Untersuchung und die praktische Durchführung aufgeklärt. Ich habe die Patienteninformationen erhalten, gelesen und verstanden. Mir wurden alle offenen Fragen beantwortet. Ich hatte ausreichend Zeit, über die Teilnahme nachzudenken. Eine Kopie dieser Einverständniserklärung erhalte ich nach Unterzeichnung.

Ich bin damit einverstanden, dass die im Rahmen der Untersuchung erhobenen Daten aufgezeichnet, wissenschaftlich ausgewertet und archiviert werden. Ich stimme ihrer Veröffentlichung unter der Voraussetzung zu, dass jeder Bezug zur Person unkenntlich gemacht wurde. Ich weiß, dass die Speicherung und Verarbeitung der Daten den Bestimmungen des Datenschutzgesetzes unterliegen. Ich bin damit einverstanden, dass unter Umständen die Aufzeichnungen über die Studie überprüft werden.

Mir ist bekannt, dass ich das Einverständnis zur Teilnahme an dieser Untersuchung jederzeit ohne Nachteile und ohne Angabe von Gründen mit sofortiger Wirkung zurückziehen kann.

Ich stimme freiwillig der Teilnahme an dieser Studie zu und werde den Pflichten innerhalb der Studie nachkommen.

Patient:

Name des Patienten in Druckbuchstaben	Unterschrift	Datum
Name der Studienleitung	Unterschrift	Datum

Appendix D

Klinik für Kinderkardiologie und
angeborene Herzfehler

Direktor: Prof. Dr. med. P. Ewert

Deutsches Herzzentrum München
des Freistaates Bayern
- Klinik an der Technischen Universität München -

Fragebogen zur Ermittlung des kardiovaskulären Risikos

Mit diesem Fragebogen werden Ihr Gesundheitszustand sowie ihr Raucherstatus ermittelt. Anhand dieser Daten und dem systolischen Blutdruck kann das Risiko errechnet werden, einen Herzinfarkt bzw. Schlaganfall innerhalb der nächsten 10 Jahre zu erleiden.
Sollten Sie bereits Fragen wie sie hier auftauchen bei der leistungsphysiologischen Untersuchung beantwortet haben, bitten wir Sie diese Fragen nochmals zu beantworten.

Vielen Dank für Ihre Mitarbeit.

PID .....

Gesundheitsstatus

	Ja	Nein
Leiden Sie an Diabetes mellitus?	○	○
Gab es bei Ihren Eltern, Großeltern oder Geschwistern einen Herzinfarkt vor dem 60. Lebensjahr?	○	○
Nehmen Sie Medikamente zur Blutdrucksenkung ein?	○	○

Raucherstatus

○ Ich habe noch nie geraucht. ○ Ich habe aufgehört zu rauchen. ○ Ich bin Raucher.

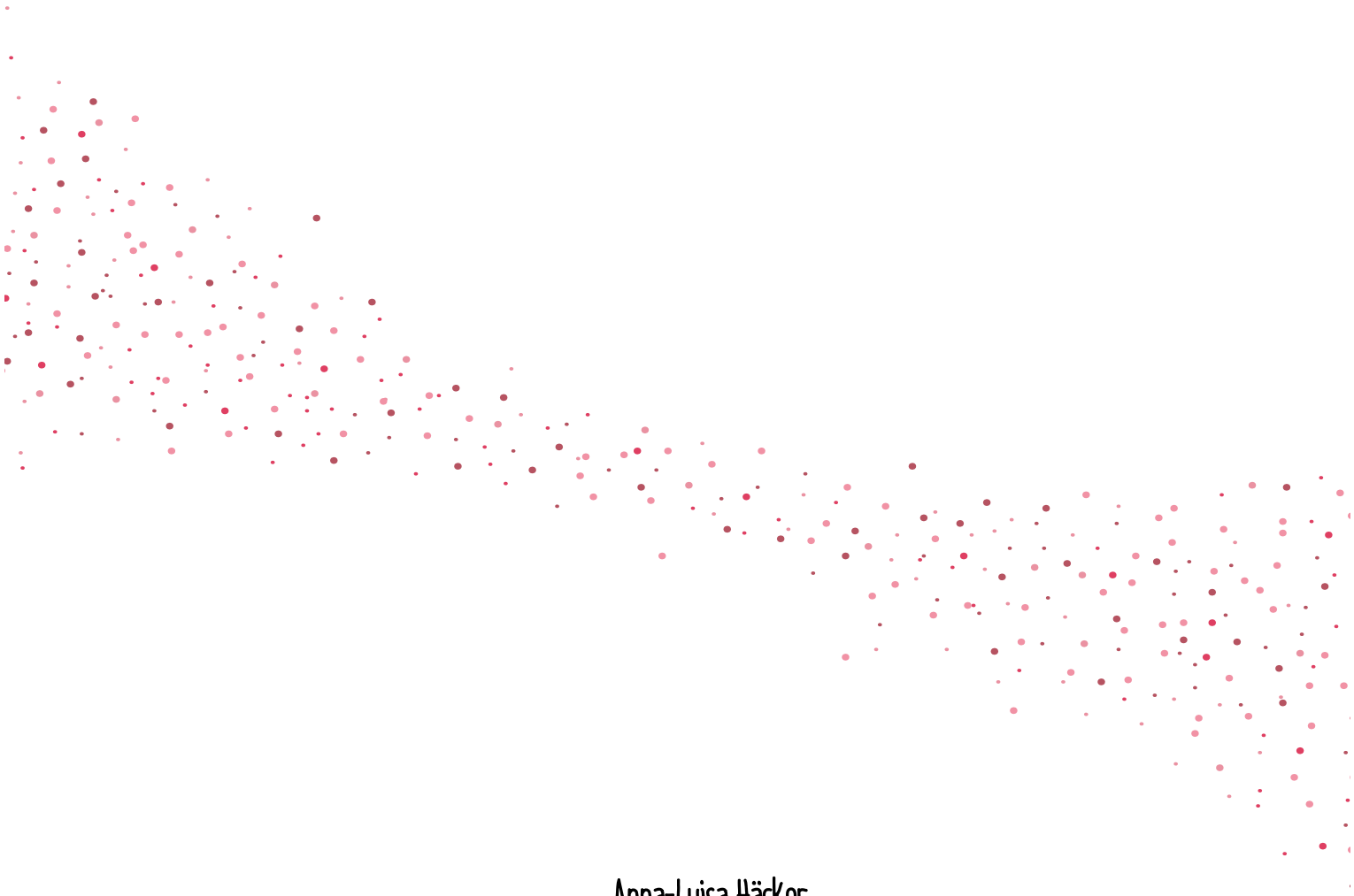
Wie lange rauchen Sie schon? / Wie lange haben Sie geraucht? ..... Jahre

Wie viele Päckchen rauchen Sie im Schnitt täglich / haben Sie geraucht? ..... Päckchen

Körperliche Aktivitäten schließen alle Tätigkeiten ein, bei denen das Herz schneller schlägt und für einige Zeit die Atmung erhöht ist. Zu den körperlichen Aktivitäten zählen beispielsweise jegliche sportliche Aktivitäten, aber auch zügigeres Gehen und auch Fußwege zu oder während der Arbeit.

Zähle Sie die gesamte Zeit zusammen, die Sie jeden Tag mit körperlichen Aktivitäten verbringen.
An wie vielen Tagen einer normalen Woche sind Sie mindestens 30 min am Tag körperlich aktiv?

⓪	①	②	③	④	⑤	⑥	⑦



Anna-Luisa Häcker