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Age-related cardiovascular risk in adult patients with congenital heart disease

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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 this particular population.

1. 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 [1]. 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 [1,2]. Despite improvements in long-term outcomes, ACHD are rarely cured and many suffer from postoperative residua and sequelae [3]. Following improved long-term outcomes, the age of ACHD increases and therefore, age-related cardiovascular diseases become a relevant risk for these patients [3–5].

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 [6–9]. Some studies in patients with CHD analyzed these single risk factors and suggested increased or abnormal values [10–17]. Increased LDL cholesterol and triglycerides along with lower HDL cholesterol were observed in ACHD [10,11] as well as a higher prevalence of metabolic syndrome and diabetes mellitus [11–14]. Furthermore, the incidence of obesity and hypertension is suggested to be higher in patients with CHD than in the reference population [11,12].

In contrast, other studies indicate no increased risk or risk factors in ACHD compared to the general population [16,17]. Overweight and obesity was less common in male ACHD than in the reference population [16], lipid profiles unobtrusive [10,18] and prevalence of coronary artery disease similar as in the general population [17].

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.

2. Patients and methods

2.1. Study subjects

All ACHD with various types of CHD were prospectively recruited during their routine follow-up appointment at the German Heart Centre in Munich from the outpatient

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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. Exclusion criteria were cognitive impairments hindering the patient to understand the task or acute infectious diseases.

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. In addition, all ACHD were grouped based on Warnes and colleagues [4] into simple, moderate and complex forms of CHD. According to this classification 76 (14.5%) had a simple, 146 (27.9%) a moderate and 301 (57.6%) a complex CHD.

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 which is registered in the 'Deutsches Register Klinischer Studien' with the number DRKS00015248.

2.2. 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 [19] but based on a German cohort of 18,460 men and 8518 women 20–78 years at study entry and followed for an average of 11.7 years [20]. 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 5 min, 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 [21,22]. 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.

2.3. 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 min? 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 min physical activity per week [23] and were categorized as "active".

2.4. 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 <0.05. Figures were created with R Studio (version 1.1.423).

3. Results

In total, 551 ACHD aged 30 years and older (43.9 ± 9.9 years, 48.3% female) were analyzed in this study. 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, Figs. 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. According to the classification of Warnes and colleagues [4], PROCAM quick check was 3.7% in simple, 2.2% in moderate and 2.1% in complex forms of CHD. The PROCAM health check was 3.3% in simple, 1.5% in moderate and 1.4% in complex forms of CHD.

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 mm Hg was present in 11.1% and increased diastolic blood pressure higher than 90 mm Hg 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 Fig. 3). Differences within the particular CHD subgroups are provided in Table 2.

Moderate-to-vigorous physical activity of at least 30 min 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).

4. 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.

4.1. 10-year risk for cardiovascular events

Only one study has analyzed the total risk of a cardiovascular event among ACDH so far [10]. Lui and colleagues [10] 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, 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 [10–17]. For example, Moons and colleagues showed in a retrospective analysis of 1976 ACHD that only 20.4% of the male and 21.0% of the female ACHD showed no cardiovascular risk factor [12]. Also Lui et al. [10] 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. In addition, other studies reported an impaired endothelial function in cyanotic CHD [24], in repaired coarctation of the aorta [25], and in patients with Fontan circulation [26].

However, studies did not discuss that atherosclerotic risk factors are also a big concern and of high prevalence in the general population [27].

4.2. Single risk factors

4.2.1. Diabetes mellitus

Altered insulin sensitivity and disordered glucose metabolism in ACHD resulting in diabetes are reported in many studies [11,12,14,18,28]. 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 [29].

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[b]
Age (years)	551	43.9 ± 9.9	45.1 ± 10.3	42.9 ± 9.4	**.008**[b]
BMI	549	25.5 ± 4.3	24.6 ± 4.4	26.3 ± 4.1	<**.001**[b]
Hip-to-waist-ratio	495	0.86 ± 0.09	0.80 ± 0.07	0.91 ± 0.07	<**.001**[b]
Systolic BP (mm Hg)	551	121.3 ± 14.9	119.0 ± 14.8	123.5 ± 14.8	<**.001**[b]
Diastolic BP (mm Hg)	551	74.7 ± 11.3	72.3 ± 10.3	77.0 ± 11.8	<**.001**[b]
		Blood lipids			
	n	All ACHD	Female ACHD (n = 195)	Male ACHD (n = 204)	p-Value[b]
LDL cholesterol (mg/dl)	445	118.9 ± 32.6	111.7 ± 30.5	121.7 ± 34.5	.070[b]
Triglyceride (mg/dl)	454	123.3 ± 71.6	111.7 ± 60.5	134.6 ± 79.6	**.001**[b]
HDL cholesterol (mg/dl)	446	59.0 ± 16.2	64.5 ± 16.6	53.6 ± 13.8	<**.001**[b]
$HbA1_c$ (%)	415	5.2 ± 0.4	5.1 ± 0.4	5.2 ± 0.5	.618[b]
		Risk factors			
	n	All ACHD	Female ACHD (n = 239)	Male ACHD (n = 266)	p-Value[c]
Diabetes mellitus (%)	551	4.0	3.0	4.9	.254[c]
Hypertensive agents (%)	551	41.7	38.0	45.3	.083[c]
Positive family history (%)	551	14.0	14.7	13.3	.653[c]
Current smoker (%)	551	10.9	9.4	12.3	.530[c]
		Risk scores					
	n	All ACHD	Reference	p-Value[a]	Female ACHD (n = 239)	Male ACHD (n = 266)	p-Value[b]
PROCAM quick check	551	2.5 ± 4.9	3.8 ± 5.2	<**.001**[a]	1.3 ± 3.4	3.6 ± 5.7	<**.001**[b]
PROCAM health check	445	1.8 ± 3.5	3.9 ± 5.3	<**.001**[a]	1.1 ± 2.8	2.5 ± 4.0	<**.001**[b]

ACHD: Adults with congenital heart disease, BMI: Body mass index, BP: blood pressure, LDL: low density lipoprotein, HDL: high density lipoprotein.
[a] *t*-Test for paired samples for the PROCAM scores between patients and reference.
[b] *t*-Test for unpaired samples between female and male adults with congenital heart disease.
[c] Chi-square test between female and male adults with congenital heart disease.

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 [14]. 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.

4.2.2. Smoking

Smoking is a major cause for cardiovascular disease due to various reasons such as increased platelet aggregability, reduced HDL cholesterol, and arboxyhemo-globinemia [30]. In our cohort of ACHD only 10.9% were smokers which is much less than in the German population with 29.7% [31]. Other studies also suggest that this major risk factor is

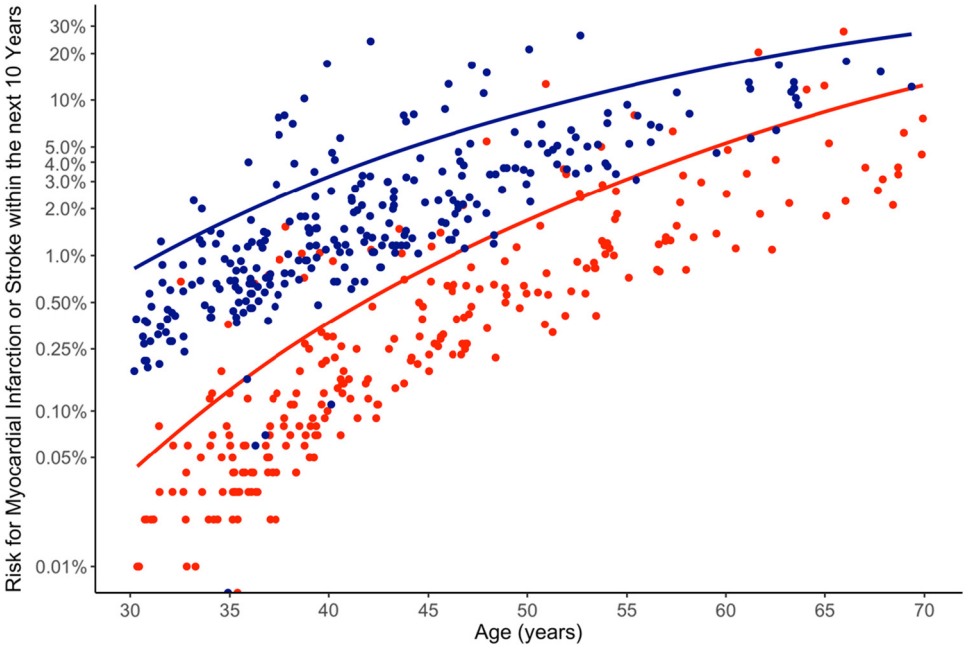

Fig. 1. PROCAM quick check in female and male ACHD and the age-related reference. Blue dots: male adults with congenital heart disease, blue line: male reference, red dots: female adults with congenital heart disease, red line: female reference, ACHD: Adults with congenital heart disease.

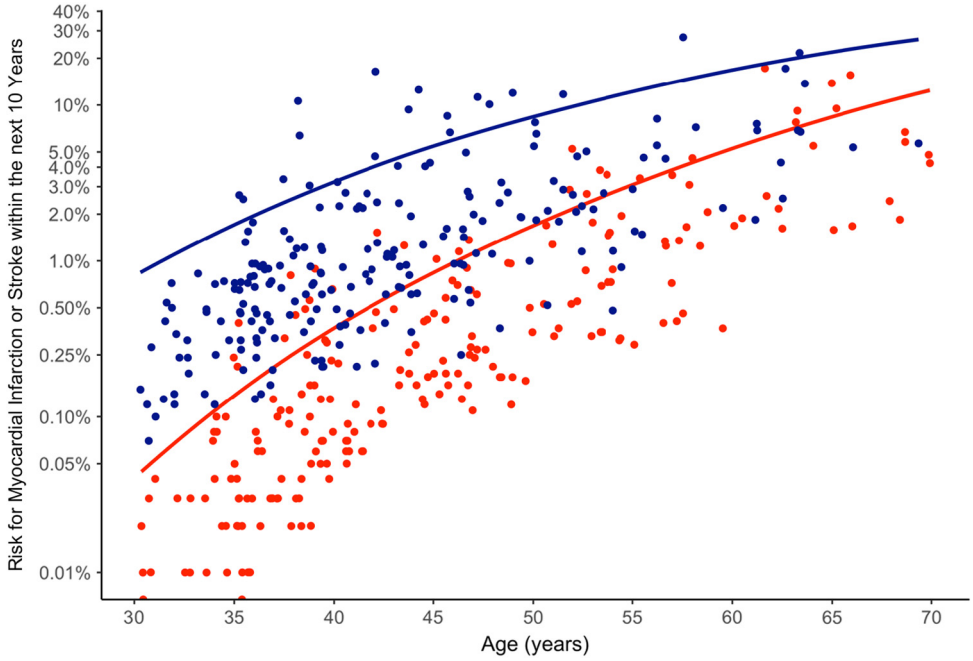

Fig. 2. PROCAM health check in female and male ACHD and the age-related reference. Blue dots: male adults with congenital heart disease, blue line: male reference, red dots: female adults with congenital heart disease, red line: female reference, ACHD: Adults with congenital heart disease.

well controlled in ACHD as prevalence is estimated at 13.5% in the Netherlands [32], 17.5% in Belgium [12], 19.4% in the UK [28], and only 2% in the US [10]. The latter might also explain the low 10-year risk of a major cardiovascular event in this study because "smoking", is one of the strongest determinants in the PROCAM score [20]. 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.

4.2.3. 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 [33]. 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 [10,18] whereas, triglycerides remained similar compared to a reference cohort [18]. HDL cholesterol was decreased in 28% [10] or significantly lower compared to a German reference cohort [18]. 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 [34].

4.2.4. Hypertension

Compared to the German reference [35], our ACHD have a lower systolic (ACHD: 121 mm Hg vs. reference: 126 mm Hg) and a slightly lower diastolic blood pressure (ACHD: 75 mm Hg vs. reference: 78 mm Hg). The difference of the blood pressure is minimal and maybe due to different measurement methods, however, the lower blood pressure might be because these patients are closely examined in a tertiary center and are diagnosed with hypertension earlier than normal hypertensive patients are. That would also explain the extensive hypertensive therapy that 42% of our patients followed. It should be considered that ACE inhibitors, diuretics or beta-blocker were often prescribed to ACHD due to other reasons than hypertension. That could have been overestimated the risk factor "hypertension" in this cohort. 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 and nevertheless, the administration of such agents has a hemodynamic effect and thus reduce cardiovascular risk.

In contrast, other studies found a higher prevalence of hypertension in ACHD [11,12] and in several ACHD subgroups higher arterial stiffness (the ability of the vessels to dilate and recoil) was found [36]. In addition, cyanotic patients, [24], patients after repaired coarctation of the aorta, [25] and patients with Fontan circulation were described with an impaired endothelial function [26].

4.2.5. 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. [16] and also Zomer and colleagues reported less obesity in all ACHD [37]. 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 [38]. 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.

4.2.6. Physical activity

Most of our ACHD cohort (56.5%) reported five or more days of physical activity and met the WHO recommendation of 150 min physical activity per week, which is above the German average of 39% [39]. This confirms objective measures from our institution [40]. 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.

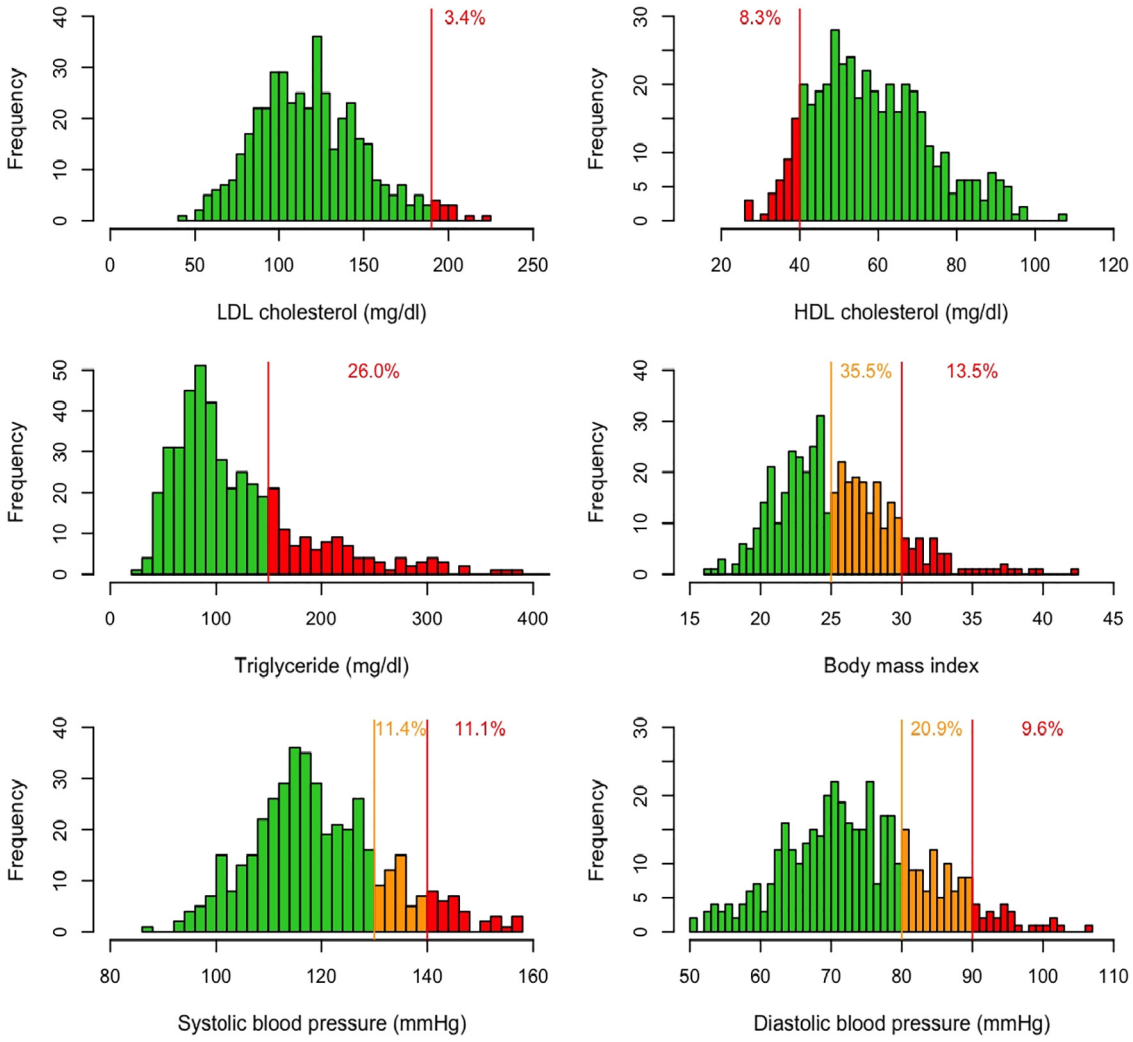

Fig. 3. Distribution of the single risk factors in all ACHD. LDL: low density lipoprotein, HDL: high density lipoprotein.

4.3. Clinical relevance

Coronary artery disease seems to be rare and not more frequent in ACHD compared to healthy controls in this study as well as described in Giannakoulas and colleagues [17]. Especially cyanotic ACHD seems to be on a lower risk for atherosclerotic cardiovascular events [41]. 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 [42]. Controversial are the results of Afilalo and colleagues outlining a large burden of atherosclerotic disease [43].

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

Table 2
Cardiovascular risk factors in ACHD regarding CHD classification.

	n	Female (%)	Age (years)	Systolic BP (mm Hg)	LDL cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL cholesterol (mg/dl)	PROCAM quick check	PROCAM health check
Aortic stenosis	60	33.3	42.0 ± 8.9	119.8 ± 11.5	128.0 ± 32.7	151.6 ± 103.6	59.3 ± 15.4	2.5 ± 4.4	2.0 ± 3.2
Coarctation of the aorta	44	40.9	41.5 ± 0.1	124.0 ± 14.9	114.4 ± 26.4	111.0 ± 55.5	61.4 ± 22.6	1.9 ± 3.4	1.1 ± 1.6
Cyanotic native/palliated	30	70.0	47.6 ± 9.6	114.9 ± 17.9	100.0 ± 30.1	109.2 ± 44.4	55.8 ± 14.6	1.2 ± 1.3	1.2 ± 2.0
Ebstein anomaly	28	57.1	50.1 ± 11.6	122.7 ± 17.8	118.2 ± 23.8	102.2 ± 47.7	62.5 ± 13.0	3.8 ± 5.9	2.0 ± 3.4
Fontan circulation	34	29.4	41.0 ± 6.7	118.1 ± 15.2	101.9 ± 28.6	115.6 ± 54.9	51.1 ± 10.3	3.1 ± 6.5	1.3 ± 2.2
Isolated shunts	101	55.4	47.7 ± 11.8	125.5 ± 15.2	126.0 ± 36.5	127.4 ± 68.0	61.0 ± 15.7	4.4 ± 7.6	3.2 ± 5.2
Pulmonary stenosis	23	56.5	46.4 ± 15.0	128.9 ± 16.1	128.7 ± 34.8	148.1 ± 73.6	58.0 ± 15.4	3.7 ± 6.7	4.7 ± 8.5
Tetralogy of Fallot	100	46.0	42.5 ± 8.6	120.3 ± 16.0	116.8 ± 27.7	119.1 ± 73.3	57.2 ± 15.4	1.6 ± 2.7	1.1 ± 1.5
TGA after Rastelli/ccTGA	27	70.4	45.0 ± 10.4	116.1 ± 13.3	118.2 ± 35.6	135.2 ± 92.8	60.7 ± 15.5	2.1 ± 3.8	1.3 ± 1.9
TGA Senning/Mustard	67	34.3	39.8 ± 4.9	119.8 ± 13.3	117.0 ± 32.6	111.7 ± 66.1	56.9 ± 16.3	1.6 ± 2.5	1.1 ± 2.0
Others	37	64.9	43.9 ± 9.6	121.5 ± 10.9	122.0 ± 37.8	128.7 ± 65.6	61.7 ± 17.9	1.3 ± 1.9	1.2 ± 2.2

ACHD: Adults with congenital heart disease, CHD: Congenital Heart Disease, TGA: Transposition of the Great Arteries, ccTGA: congenital corrected Transposition of the Great Arteries, BP: blood pressure, LDL: low density lipoprotein, HDL: high density lipoprotein.

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 [44]. Likewise, it is not clear how premature stiffening of the arterial vessels contributes to heart failure and atherosclerosis in this patient population [36].

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.

5. 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.

6. Limitations

The PROCAM has not been prospectively validated in patients with CHD and these calculators have been criticized as underestimate cardiovascular risk in specialized populations [45].

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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References

[1] E.J. Benjamin, M.J. Blaha, S.E. Chiuve, M. Cushman, S.R. Das, R. Deo, et al., Heart disease and stroke statistics-2017 update: a report from the American Heart Association, Circulation 135 (10) (2017) e146–e603.
[2] G.P. Diller, A. Kempny, R. Alonso-Gonzalez, L. Swan, A. Uebing, W. Li, et al., Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre, Circulation 132 (22) (2015) 2118–2125.
[3] C.A. Warnes, The adult with congenital heart disease: born to be bad? J. Am. Coll. Cardiol. 46 (1) (2005) 1–8.
[4] C.A. Warnes, R. Liberthson, G.K. Danielson, A. Dore, L. Harris, J.I. Hoffman, et al., Task force 1: the changing profile of congenital heart disease in adult life, J. Am. Coll. Cardiol. 37 (5) (2001) 1170–1175.
[5] O. Tutarel, Acquired heart conditions in adults with congenital heart disease: a growing problem, Heart 100 (17) (2014) 1317–1321.
[6] D. Goff Jr., D. Lloyd-Jones, G. Bennett, S. Coady, R. D'Agostine Sr., R. Gibbons, et al., ACC/AHA guideline on the assessment of cardiovascular risk: a report of the ACC/AHA Task Force on Practice Guidelines, J. Am. Coll. Cardiol. 63 (Pt B) (2013) 2935–2959.
[7] G.S. Berenson, S.R. Srinivasan, W. Bao, W.P. Newman, R.E. Tracy, W.A. Wattigney, Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults, N. Engl. J. Med. 338 (23) (1998) 1650–1656.
[8] S. Yusuf, S. Hawken, S. Ounpuu, T. Dans, A. Avezum, F. Lanas, et al., Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study, Lancet 364 (9438) (2004) 937–952 (London, England).
[9] B.F. Voight, G.M. Peloso, M. Orho-Melander, R. Frikke-Schmidt, M. Barbalic, M.K. Jensen, et al., Plasma HDL cholesterol and risk of myocardial infarction: a Mendelian randomisation study, Lancet 380 (9841) (2012) 572–580.
[10] G.K. Lui, I.S. Rogers, V.Y. Ding, H.K. Hedlin, K. MacMillen, D.J. Maron, et al., Risk estimates for atherosclerotic cardiovascular disease in adults with congenital heart disease, Am. J. Cardiol. 119 (1) (2017) 112–118.
[11] J.R. Moon, J. Song, J. Huh, I. Kang, S.W. Park, S.-A. Chang, et al., Analysis of cardiovascular risk factors in adults with congenital heart disease, Korean Circ. J. 45 (5) (2015) 416–423.
[12] P. Moons, K.V. Deyk, D. Dedroog, E. Troost, W. Budts, Prevalence of cardiovascular risk factors in adults with congenital heart disease, Eur. J. Cardiovasc. Prev. Rehabil. 13 (4) (2006) 612–616.
[13] J.F. Deen, E.V. Krieger, A.E. Slee, A. Arslan, D. Arterburn, K.K. Stout, et al., Metabolic syndrome in adults with congenital heart disease, J. Am. Heart Assoc. 5 (2) (2016), e001132.
[14] N.L. Madsen, B.S. Marino, J.G. Woo, R.W. Thomsen, J. Videbœk, H.B. Laursen, et al., Congenital heart disease with and without cyanotic potential and the long-term risk of diabetes mellitus: a population-based follow-up study, J. Am. Heart Assoc. 5 (7) (2016), e003076.
[15] H. Ohuchi, Y. Miyamoto, M. Yamamoto, H. Ishihara, H. Takata, A. Miyazaki, et al., High prevalence of abnormal glucose metabolism in young adult patients with complex congenital heart disease, Am. Heart J. 158 (1) (2009) 30–39.
[16] C. Sandberg, D. Rinnström, M. Dellborg, U. Thilén, P. Sörensson, N.-E. Nielsen, et al., Height, weight and body mass index in adults with congenital heart disease, Int. J. Cardiol. 187 (2015) 219–226.
[17] G. Giannakoulas, K. Dimopoulos, R. Engel, O. Goktekin, Z. Kucukdurmaz, M.A. Vatankulu, et al., Burden of coronary artery disease in adults with congenital heart disease and its relation to congenital and traditional heart risk factors, Am. J. Cardiol. 103 (10) (2009) 1445–1450.
[18] E. Martínez-Quintana, F. Rodríguez-González, V. Nieto-Lago, F.J. Nóvoa, L. López-Rios, M. Riaño-Ruiz, Serum glucose and lipid levels in adult congenital heart disease patients, Metab. Clin. Exp. 59 (11) (2010) 1642–1648.
[19] R.B. D'Agostino Sr., R.S. Vasan, M.J. Pencina, P.A. Wolf, M. Cobain, J.M. Massaro, et al., General cardiovascular risk profile for use in primary care: the Framingham Heart Study, Circulation 117 (6) (2008) 743–753.
[20] G. Assmann, P. Cullen, H. Schulte, Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study, Circulation 105 (3) (2002) 310–315.
[21] M.F. Piepoli, A.W. Hoes, S. Agewall, C. Albus, C. Brotons, A.L. Catapano, et al., 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), Atherosclerosis 252 (2016) 207–274.
[22] A.L. Catapano, I. Graham, G. De Backer, O. Wiklund, M.J. Chapman, H. Drexel, et al., 2016 ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), Atherosclerosis 253 (2016) 281–344.
[23] World Health Organization, Global Recommendations on Physical Activity for Health, http://wwwwhoint/dietphysicalactivity/factsheet_recommendations/en/ 2012.
[24] R.L. Cordina, S. Nakhla, S. O'Meagher, J. Leaney, S. Graham, D.S. Celermajer, Widespread endotheliopathy in adults with cyanotic congenital heart disease, Cardiol. Young 25 (3) (2015) 511–519.
[25] S. Brili, D. Tousoulis, C. Antoniades, C. Aggeli, A. Roubelakis, S. Papathanasiu, et al., Evidence of vascular dysfunction in young patients with successfully repaired coarctation of aorta, Atherosclerosis 182 (1) (2005) 97–103.
[26] S.M. Jin, C.I. Noh, E.J. Bae, J.Y. Choi, Y.S. Yun, Impaired vascular function in patients with Fontan circulation, Int. J. Cardiol. 120 (2) (2007) 221–226.
[27] T. Tiffe, M. Wagner, V. Rucker, C. Morbach, G. Gelbrich, S. Stork, et al., Control of cardiovascular risk factors and its determinants in the general population- findings from the STAAB cohort study, BMC Cardiovasc. Disord. 17 (1) (2017) 276.
[28] J. Billett, M.R. Cowie, M.A. Gatzoulis, I.F. Vonder Muhll, A. Majeed, Comorbidity, healthcare utilisation and process of care measures in patients with congenital heart disease in the UK: cross-sectional, population-based study with case-control analysis, Heart 94 (9) (2008) 1194–1199.
[29] C. Heidemann, Y. Du, I. Schubert, W. Rathmann, C. Scheidt-Nave, Prävalenz und zeitliche Entwicklung des bekannten diabetes mellitus, Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 56 (5–6) (2013) 668–677.
[30] R.S. Shah, J.W. Cole, Smoking and stroke: the more you smoke the more you stroke, Expert. Rev. Cardiovasc. Ther. 8 (7) (2010) 917–932.
[31] T. Lampert, E. von der Lippe, S. Müters, Verbreitung des Rauchens in der Erwachsenenbevölkerung in Deutschland, Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 56 (5–6) (2013) 802–808.

[32] P.M. Engelfriet, W. Drenthen, P.G. Pieper, J.G. Tijssen, S.C. Yap, E. Boersma, et al., Smoking and its effects on mortality in adults with congenital heart disease, Int. J. Cardiol. 127 (1) (2008) 93–97.
[33] C. Scheidt-Nave, Y. Du, H. Knopf, A. Schienkiewitz, T. Ziese, E. Nowossadeck, et al., Verbreitung von Fettstoffwechselstörungen bei Erwachsenen in Deutschland, Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 56 (5–6) (2013) 661–667.
[34] J.B. Tarp, A.S. Jensen, T. Engstrom, N.H. Holstein-Rathlou, L. Sondergaard, Cyanotic congenital heart disease and atherosclerosis, Heart 103 (12) (2017) 897–900.
[35] H. Neuhauser, C. Diederichs, H. Boeing, S.B. Felix, C. Jünger, R. Lorbeer, et al., Hypertension in Germany: data from seven population-based epidemiological studies (1994–2012), Dtsch Arztebl Int 113 (48) (2016) 809.
[36] A.-L. Häcker, B. Reiner, R. Oberhoffer, A. Hager, P. Ewert, J. Müller, Increased arterial stiffness in children with congenital heart disease, Eur. J. Prev. Cardiol. 25 (1) (2018) 103–109.
[37] A.C. Zomer, I. Vaartjes, C.S. Uiterwaal, E.T. van der Velde, G.J. Sieswerda, E.M. Wajon, et al., Social burden and lifestyle in adults with congenital heart disease, Am. J. Cardiol. 109 (11) (2012) 1657–1663.
[38] M. Brida, K. Dimopoulos, A. Kempny, E. Liodakis, R. Alonso-Gonzalez, L. Swan, et al., Body mass index in adult congenital heart disease, Heart 103 (16) (2017) 1250–1257.
[39] World health Organization, Germany - Physical Activity Factsheet, http://www.euro.who.int/__data/assets/pdf_file/0010/288109/GERMANY-Physical-Activity-Factsheet.pdf?ua=12015 (cited 2018).
[40] J. Müller, J. Hess, A. Hager, Daily physical activity in adults with congenital heart disease is positively correlated with exercise capacity but not with quality of life, Clin. Res. Cardiol. 101 (1) (2012) 55–61.
[41] A. Giamberti, M. Lo Rito, E. Conforti, A. Varrica, M. Carminati, A. Frigiola, et al., Acquired coronary artery disease in adult patients with congenital heart disease: a true or a false problem? J. Cardiovasc. Med. (Hagerstown) 18 (8) (2017) 605–609.
[42] A.C. Zomer, C.S. Uiterwaal, E.T. van der Velde, J.G. Tijssen, E.C. Mariman, C.L. Verheugt, et al., Mortality in adult congenital heart disease: are national registries reliable for cause of death? Int. J. Cardiol. 152 (2) (2011) 212–217.
[43] J. Afilalo, J. Therrien, L. Pilote, R. Ionescu-Ittu, G. Martucci, A.J. Marelli, Geriatric congenital heart disease: burden of disease and predictors of mortality, J. Am. Coll. Cardiol. 58 (14) (2011) 1509–1515.
[44] S.L. Roche, C.K. Silversides, Hypertension, obesity, and coronary artery disease in the survivors of congenital heart disease, Can. J. Cardiol. 29 (7) (2013) 841–848.
[45] A.M. Thompson-Paul, K.A. Lichtenstein, C. Armon, F.J. Palella Jr., J. Skarbinski, J.S. Chmiel, et al., Cardiovascular disease risk prediction in the HIV outpatient study, Clin. Infect. Dis. 63 (11) (2016) 1508–1516.