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Metabolic syndrome in adults with congenital heart disease and increased intima-media thickness

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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 the metabolic syndrome (MetS) impact the risk of increased carotid intima-media thickness (cIMT) and thereby long-term 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, 512 ACHD (43.0 ± 9.6 years, 48.9% female) were screened for MetS by the standards of the International Diabetes Federation, and their cIMT by ultrasound from January 2017 to June 2019. MetS was prevalent in 72 (14.1%) of the ACHD population (34 female, 15.5%). Regarding severity class, patients with simple forms of CHD had a MetS prevalence of 11.8%, moderate 16.7%, and severe 13.8%. ACHD with MetS had significantly increased cIMT compared to ACHD without MetS (ACHD with MetS: 0.587 ± 0.079 mm, ACHD without MetS: 0.560 ± 0.087 mm, mean difference: 0.028 mm, P = .013). Such a difference in vascular structure corresponds to roughly five 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
carotid intima-media thickness, congenital heart disease, metabolic syndrome

1 | 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.[1-3]

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,[4] which—depending on the definition criteria—10%-40% of people suffer from worldwide.[5] 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.[6] Consequences of MetS are triggered among others by elevated levels of pro-inflammatory markers and activated sympathetic nervous and renin-angiotensin system leading to pathophysiologic changes such as atherosclerosis and vascular calcification.[7] MetS is therefore a major risk factor for age-related cardiovascular diseases and diabetes type 2,[6,8] and

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associated with an increased cardiovascular and all-cause mortality and morbidity.[8-11] Unfortunately, there is evidence that the prevalence of MetS is higher in ACHD than in healthy controls.[12,13]

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[14] and therefore a risk factor for cardiovascular diseases,[15,16] and is further associated with the risk of cognitive impairment.[17]

So far, the association of atherosclerotic and vascular proliferation due to 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.

2 | PATIENTS AND METHODS

2.1 | Study subjects

From January 2017 to June 2019, 512 ACHD aged 30 years and older (43.0 ± 9.6 years, 48.9% 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,[18] 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.

2.2 | Metabolic Syndrome (MetS)

MetS was defined as existent when the patient met three or more criteria displayed in Table 2. This definition corresponds to the criteria of the International Diabetes Federation[8] with the only adaption of haemoglobin $A1_c$ ($HbA1_c$) instead of fasting plasma glucose.

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 measurement criteria of the World Health Organization and the International Diabetes Federation.[19] Population- and country-specific values for Caucasians were a waist circumference of 102 cm for men and 88 cm in women.[8]

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 5 minutes. With an arm-adjusted cuff size, the blood pressure was measured at the left upper arm. History of hypertension, systolic blood pressure 130

TABLE 1 ACHD subgroups and severity classes and the prevalence of MetS

	Subgroups		
	n	Prevalence of MetS (%)	Age (years)
Aortic stenosis	55	9.1	41.5 ± 9.1
Coarctation of the aorta	44	18.2	41.9 ± 8.3
Cyanotic patients (native or palliated)	25	28.0	45.9 ± 8.7
Ebstein anomaly	21	14.3	47.9 ± 12.6
Fontan circulation	19	15.8	40.4 ± 6.6
Isolated shunts[a]	102	16.7	47.7 ± 11.7
Pulmonary stenosis	21	19.0	44.3 ± 13.2
Tetralogy of Fallot	97	8.2	42.3 ± 8.0
TGA after Rastelli repair and ccTGA	25	16.0	43.6 ± 10.6
TGA after Senning or Mustard	63	11.1	39.0 ± 4.6
Others	4	15.0	44.3 ± 9.9
	Severity class[b]		
	n	Prevalence of MetS (%)	Age (years)
Simple	76	11.8	47.9 ± 12.8
Moderate	155	16.7	43.4 ± 9.5
Severe	268	13.8	42.1 ± 8.5

Abbreviations: ccTGA, congenital corrected Transposition of the Great Arteries; TGA: Transposition of the Great Arteries.
[a]Including atrial, ventricular, and atrioventricular septal defect.
[b]Severity classes according to Warnes and colleagues.[18]

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 mm Hg	≥130 mm Hg
or diastolic blood pressure	≥85 mm Hg	≥85 mm Hg
or hypertensive therapy	Yes	Yes
Hemoglobin $A1_c$ ($HbA1_c$)	≥5.7%	≥5.7%
or previously diagnosed diabetes	Yes	Yes

mm Hg or higher and diastolic blood pressure of 85 mm Hg or any hypertensive treatment, was considered as meeting the criterion for MetS.

Plasma samples for triglycerides, HDL cholesterol, and HbA1c measurements were drawn from an antecubital vein in sitting position in a non-fasting state.[20] To analyze 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 criterion. MetS criteria in women were HDL cholesterol <40 mg/dL and in men <50 mg/dL cholesterol.

As already mentioned, fasting plasma glucose was substituted by $HbA1_c$ for defining MetS. The American Diabetes Association[21] 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" can 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 determining MetS.[22] Therefore, a value of 5.7% or higher was considered meeting the MetS criterion.

2.3 | 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.[14] 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 (120°, 150°, 210°, 240°) was calculated. The measurements were performed by two different sonographers who both had the same training. The results were regularly cross-checked by both sonographers.

2.4 | Data analyses

Anthropometric data of ACHD patients are reported 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. Differences for the IMT between ACHD with and without MetS were first calculated with a t-test for unpaired samples, and second by performing a general linear model 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).

3 | RESULTS

MetS was prevalent in 72 (14.1%) of the ACHD. In female ACHD 34 (15.5%) and in male ACHD 38 (17.2%) had MetS. Regarding the severity classes according to Warnes and colleagues,[18] simple forms of CHD had a MetS prevalence of 11.8%, moderate 16.7%, and severe 13.8% (Table 1).

Concerning the single risk factors, waist circumference was increased in 102 (20.4%), triglycerides in 134 (26.2%), and HDL in 67 (13.2%), and diabetes mellitus was prevalent in 31 (6.1%). About 292 (57.3%) patients met our blood pressure criterion. Where 93 (18.3%) had systolic blood pressure of 130 mm Hg or higher or a diastolic blood pressure of 85 mm Hg, and the other 199 (39.0%) received hypertensive treatment. Risk factors and anthropometric data for ACHD with and without MetS are displayed in Table 1 and Figure 1.

The cIMT was significantly increased in ACHD with MetS compared to ACHD without MetS calculated with a t-test (ACHD with MetS: 0.606 ± 0.138 mm, ACHD without MetS: 0.558 ± 0.095 mm, mean difference: 0.048 mm, $P = .011$) and the general linear model (ACHD with MetS: 0.587 ± 0.079 mm, ACHD without MetS: 0.560 ± 0.087 mm, mean difference: 0.028 mm, $P = .013$) (Table 3, Figure 2). This difference corresponds to 4.9 years of normal vascular aging between ACHD with and without MetS. The CHD severity classes had no significant impact on the cIMT in ACHD with MetS compared to ACHD without MetS.

4 | DISCUSSION

In our study, ACHD with MetS had a greater cIMT compared to ACHD patients without MetS. That change in vessel structure roughly corresponds to 5 years of normal vascular aging of the vessels.

In this study, 14.1% of the ACHD were diagnosed with a MetS, which seems slightly lower compared to 21.5% of the 40- to 49-year-old cohort of the population-based sample in Germany.[23] In contrast, the study of Deen and colleagues demonstrated 15.0% of the ACHD had a MetS and the prevalence was twice as high as in the population-based sample.[12] Regarding the severity classes according to Warnes and colleagues,[18] simple forms of CHD had a MetS prevalence of 11.8%, moderate 16.7%, and severe 13.8% in this study. In comparison to Deen and colleagues,[12] 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% to 39% depending on eight different MetS definitions.[24] 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

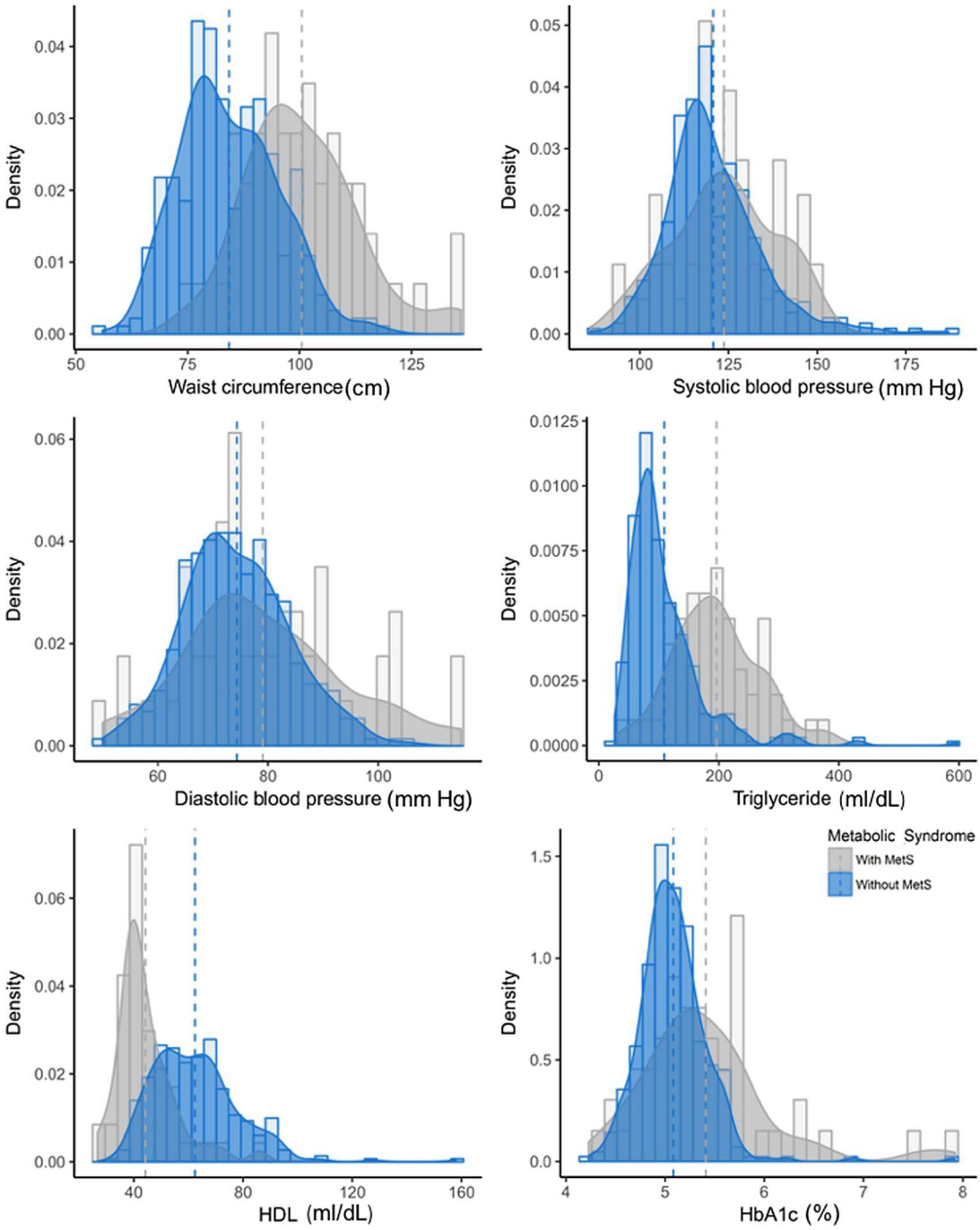

FIGURE 1 ACHD with MetS and without MetS and the distributions of the single risk factors

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.[25] Furthermore, several studies found decreased insulin sensitivity, abnormal glucose tolerance, and low high-density lipoprotein levels in their ACHD cohort.[12,26,27] A recent study further suggest a different lipid metabolism in cyanotic patients as seen in low LDL and total cholesterol levels.[27] 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.[26] However, since metabolism seems to be different in this population in general, it makes sense to focus on different aspects within the examined cohort instead of comparing the data of ACHD 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 0.028 mm higher compared to ACHD without MetS. Normal vascular aging is

TABLE 3 ACHD with and without MetS and cIMT

Anthropometric data	ACHD with MetS (*n* = 72)	ACHD without MetS (*n* = 440)		*P* value[a]
Age (years)	46.4 ± 10.2	43.0 ± 9.6		.011[a]
BMI	28.8 ± 4.6	24.4 ± 3.5		<.001[a]
Waist circumference (cm)	100.3 ± 12.8	83.8 ± 10.6		<.001[a]
Systolic BP (mm Hg)	125.4 ± 13.9	120.4 ± 13.4		.004[a]
Diastolic BP (mm Hg)	79.0 ± 13.8	74.4 ± 9.6		.001[a]
Blood lipids	**ACHD with MetS (*n* = 72)**	**ACHD without MetS (*n* = 440)**		***P* value[a]**
Triglyceride (mg/dL)	193.6 ± 70.2	108.5 ± 61.7		<.001[a]
HDL (mg/dL)	45.2 ± 11.3	62.1 ± 15.1		<.001[a]
$HbA1_c$ (%)	5.4 ± 0.6	5.1 ± 0.3		<.001[a]
Carotid intima-media thickness	**ACHD with MetS (*n* = 72)**	**ACHD without MetS (*n* = 440)**	**Mean difference**	***P* value[b]**
Carotid intima-media thickness (mm)	0.587 ± 0.079	0.560 ± 0.087	0.028	.012[b]

Abbreviations: ACHD, adults with congenital heart disease; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein cholesterol; MetS, metabolic syndrome.
[a]*T*-test for unpaired samples between ACHD with MetS and without MetS.
[b]General linear model with adjusting for sex and age between ACHD with MetS and without MetS.

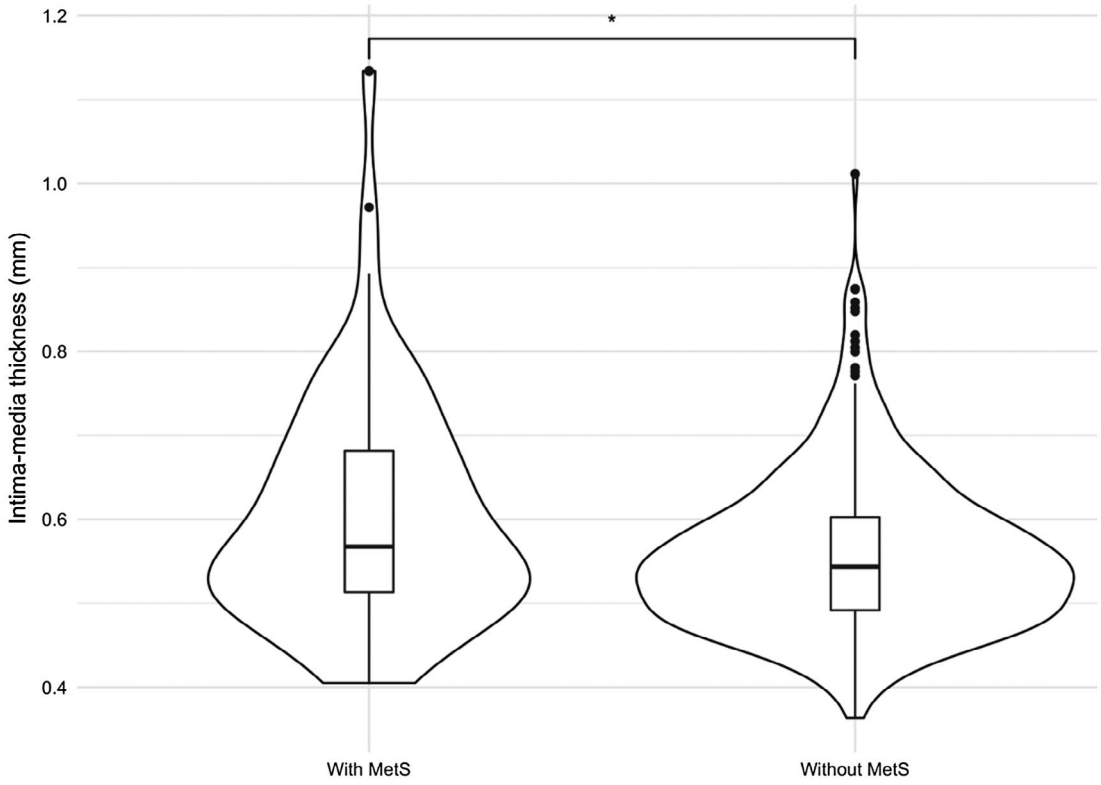

FIGURE 2 ACHD with MetS and without MetS and their intima-media thickness. MetS, metabolic syndrome

characterized by a cIMT increase of 0.0057 mm per year[28] which is equivalent to an age difference of 4.9 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 toward 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.[29] 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.[30] 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.[16,31] 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.[16]

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[12] and especially in those ACHD already having cardiovascular risk factors, as the risk of secondary diseases might be also increased in ACHD.

5 | 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.

6 | 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.[20]

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. We have therefore re-analyzed all patients who were diagnosed with a MetS due to the risk factor "blood pressure." When only those with proven hypertension and hypertensive medication due to hypertension were classified, only 67 instead of 72 remain in the MetS group. Recalculation of the general linear model provides with 0.029 mm IMT difference instead of 0.028 mm the same significant result. 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. For that reason, we decided to stick to our previously defined criteria from the methods.

Even though both sonographers had regular training in measuring IMT, it could not be ruled out that variability between measurements exist.

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 general population.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Häcker sampled the data in the study center, analyzed the data, and drafted the first version of the manuscript.

Oberhoffer, Hager, and Ewert contributed to study conception and design and gave important input for revising and improving the quality of the manuscript.

Müller was responsible for conception and design of the study and was responsible for data monitoring and integrity.

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