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Challenges in the Long-Term Care of Adults with Congenital Heart Disease: Gender/Sex-Differences, Aortopathies, and Cardiac Rehabilitation

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Summary

Few areas of modern medicine have seen as much success as the area of congenital heart disease (CHD), which includes the most common isolated organ abnormalities worldwide. Due to various advances in modern medicine, today, up to 97% of children in the industrialized world with CHD reach adulthood and have an increasingly better quality of life. In Germany, about 330,000 adults are currently living with CHD. Despite all medical advances, a complete correction of the CHD is rarely possible. Therefore, the term “repair” is used rather than “correction”. Consequently, the majority of adults with CHD (ACHD) are chronically ill, from residua, sequelae, complications, and acquired cardiac or non-cardiac comorbidities, all of which may negatively affect morbidity and mortality. With few exceptions, lifelong dedicated follow-up with experienced healthcare professionals is therefore necessary. Compared with knowledge on adults with acquired heart disease, many more research gaps exist regarding ACHD, particularly regarding sex/gender differences, aortopathies, and rehabilitation measures.

This dissertation presents data from three scientific studies the author has conducted and published internationally on current care practices for ACHD: the first on sex/gender differences, the second on aortopathies, and the third on rehabilitation. The first study (*Article 1*) was to our knowledge the first in the literature to examine the association between patient-reported outcome measures (PROMs) and sex differences in a large ACHD cohort. The first and second studies (*Articles 1 and 2)* revealed major knowledge deficits that were previously unknown among both patients themselves and their primary care physicians regarding the need for lifelong specialized medical follow-up. This was reflected in a high unmet need for counseling among patients. As a consequence of our data, it is now clear that it is of particular importance to alert both patients and their primary care physicians to the need for lifelong specialized followup, including, among other CHD-specific problems, aortopathies and gender-specific management. In order to further reduce cardiac morbidity and mortality, medical rehabilitation is another important component of ACHD healthcare. For this reason, the third study (*Article 3*) focused on rehabilitation measures in ACHD. It provides, for the first time, major data on the course of rehabilitation in a large ACHD cohort after surgical or interventional treatment. Rehabilitation resulted in an overall improvement of cardiovascular risk factors, reduction in prescription of medication, and reintegration into the employment process. It is also important to mention that no life-threatening events occurred during rehabilitation, even in ACHD with complex cases. However, the study also highlights that many ACHD cannot be rehabilitated in the same way as patients with acquired heart disease. Therefore, a close collaboration between the rehabilitation facility and ACHD-certified congenital cardiologists or ACHD centers is required.

Zusammenfassung

Kaum ein anderes Gebiet der modernen Medizin hat so große Erfolge zu verzeichnen wie die Behandlung von angeborenen Herzfehlern (AHF), den weltweit häufigsten, isolierten Organanomalien. Aufgrund der enormen Fortschritte der modernen Medizin erreichen in der industrialisierten Welt etwa 97% der Kinder mit AHF das Erwachsenenalter. So leben in Deutschland mittlerweile etwa 330.000 Erwachsene mit angeborenen Herzfehlern (EMAH). Trotz dieser Fortschritte und einer zunehmend besseren Lebensqualität sind alle Patienten mit AHF aufgrund von anatomischen und/oder funktionellen Rest- und Folgezuständen, Komplikationen sowie kardialen und nicht-kardialen Begleiterkrankungen (Co-Morbiditäten) chronisch herzkrank und bedürfen einer kontinuierlichen, lebensbegleitenden Nachsorge durch erfahrene Spezialisten. Mehr noch als bei erworbenen Herzerkrankungen bestehen bei AHF Forschungslücken, u.a. in Bezug auf Geschlechtsunterschiede, Aortopathien und Rehabilitationsmaßnahmen.

Im Rahmen dieser Dissertation wurden daher diese drei Bereiche wissenschaftlich aufgearbeitet und die Ergebnisse international in peer-reviewed Journalen veröffentlicht. Dabei wurde jeweils einer der oben genannten Bereiche vor dem Hintergrund der aktuellen Versorgungssituation von EMAH untersucht. Im ersten Artikel konnten erstmalig „patient-reported outcome measures“ (PROMs) zu geschlechterspezifischen Unterschieden in einem großen EMAH-Kollektiv erhoben werden. Die ersten beiden Artikel haben zudem gezeigt, dass sowohl bei den Patienten selbst, als auch bei deren primärversorgenden Ärzten, große Wissendefizite hinsichtlich der Notwendigkeit einer lebenslangen spezialisierten Nachsorge bestehen. Dies spiegelte sich in einem hohen ungedeckten Beratungsbedarf der Patienten wider. Für die Zukunft ist es von besonderer Bedeutung, sowohl Patienten als auch deren Primärversorger auf AHF-spezifische Probleme wie Aortopathien oder ein geschlechter-spezifisches Behandlungsmanagement und die damit verbundene Notwendigkeit einer lebenslangen spezialisierten Nachsorge aufmerksam zu machen. Dabei müssen herzfehler-spezifische Besonderheiten, wie z.B. Aortopathien oder Geschlechterunterschiede, im Rahmen der jeweiligen AHF besonders beachtet werden. Um die kardiale Morbidität und Mortalität niedrig halten zu können, ist eine medizinische Rehabilitation, insbesondere nach operativen oder interventionellen Eingriffen, ein wichtiger Bestandteil des Gesundheitswesens. Aus diesem Grund befasst sich der dritte Artikel mit Rehabilitations-maßnahmen bei EMAH und liefert erstmalig vergleichbare Daten zum Verlauf einer Rehabilitation in einem großen EMAH-Kollektiv. Die Rehabilitationsmaßnahmen verliefen dabei ohne gravierende Zwischenfälle und führten insgesamt zu einer Verbesserung kardiovaskulärer Risikofaktoren, einer Medi-kamenten-Reduktion und zur Wiedererlangung der Arbeitsfähigkeit. Allerdings macht die Studie auch deutlich, dass EMAH nicht in identischer Form wie Patienten mit erworbenen Herzerkrankungen behandelt werden können und daher

eine enge Kooperation zwischen der Rehabilitationseinrichtung sowie EMAH-zertifizierten congenital-kardiologischen Experten oder Zentren notwendig ist.

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Abbreviations

ACHD	adults with congenital heart disease
AS	aortic stenosis, congenital
ASD	atrial septal defect
AVSD	atrio-ventricular septal defect
BAV	bicuspid aortic valve
CCTGA	congenitally corrected transposition of the great arteries
CHD	congenital heart defect/disease
CoA	coarctation of the aorta
CVA	cerebrovascular accident
CT	computed tomography
DORV	double-outlet right ventricle
GPP	good pharmacoepidemiological practice
HOCM	hypertrophic obstructive cardiomyopathy
ICD	implantable cardioverter defibrillator
MFS	Marfan-Syndrome
MRI	magnetic resonance imaging
OR	odds ratio
PA	pulmonary atresia
PCP	primary care provider
PH	pulmonary hypertension
PROM	patient reported outcome measure
TAC	truncus arteriosus communis
TGA	transposition of the great arteries
TIA	transient ischemic attack
TOF	tetralogy of Fallot
TrA	tricuspid atresia
TTE	transthoracic echocardiography
VEmaH	German acronym for "medical care situation of ACHD"
VSD	ventricular septal defect

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Notes

Throughout the thesis, gender-specific terms may be used in order to ease the text flow. Whenever a gender-specific term is used, it should be understood as referring to both genders, unless explicitly stated.

1 Introduction

Congenital heart defects (CHD) are defined as „*any type of congenital defect in one or more structures of the heart or blood vessels, or a hereditary disorder involving the heart and/or the great arteries (e.g. Marfan syndrome or Fabry disease)*“ (1).

Worldwide, approximately 1.35 million children are born each year with CHD, the most common of all isolated organ abnormalities (2, 3). Reported incidence rates differ, mostly due to different geographics, survey period, ethnicity, and disease definition. Recent studies and registry data postulate a significantly higher incidence of CHD than previously expected, ranging from 8 to 14 per 1,000 live births (2, 4-12).

According to the recommendations of the European Society of Cardiology, CHD lesions can be categorized on the basis of severity into mild, moderate, and severe (*Table 1*) (13).

Table 1: *Classification of congenital heart defects according to complexity*, adapted from (13)

Mild	- Isolated congenital aortic valve disease and bicuspid aortic disease - Isolated congenital mitral valve disease (except parachute valve, cleft leaflet) - Mild isolated pulmonary stenosis (infundibular, valvular, supravalvular) - Isolated small ASD, VSD, or PDA - Repaired secundum ASD, sinus venosus defect, VSD, or PDA without residuae or sequellae, such as chamber enlargement, ventricular dysfunction, or elevated PAP
Moderate*	- Anomalous pulmonary venous connection (partial or total) - Anomalous coronary artery arising from the PA - Anomalous coronary artery arising from the opposite sinus - Aortic stenosis - subvalvular or supravalvular - AVSD, partial or complete, including primum ASD (excluding pulmonary vascular disease) - ASD secundum, moderate or large unrepaired (excluding pulmonary vascular disease) - Coarctation of the aorta - Double chambered right ventricle - Ebstein anomaly - Marfan syndrome and related HTAD, Turner Syndrome

	- PDA, moderate or large unrepaired (excluding pulmonary vascular disease) - Peripheral pulmonary stenosis - Pulmonary stenosis (infundibular, valvular, supravalvular), moderate or severe - Sinus of Valsalva aneurysm/fistula - Sinus venosus defect - Tetralogy of Fallot – repaired - Transposition of the great arteries after arterial switch operation - VSD with associated abnormalities (excluding pulmonary vascular disease) and/or moderate or greater shunt
Severe*	- Any CHD (repaired or unrepaired) associated with pulmonary vascular disease (including Eisenmenger syndrome) - Any cyanotic CHD (unoperated or palliated) - Double-outlet ventricle - Fontan circulation - Interrupted aortic arch - Pulmonary atresia (all forms) - Transposition of the great arteries (except for patients with arterial switch operation) - Univentricular heart (including double inlet left/right ventricle, tricuspid/mitral atresia, hypoplastic left heart syndrome, any other anatomic abnormality with a functionally single ventricle) - Truncus arteriosus - Other complex abnormalities of AV and ventriculoarterial connection (i.e. crisscross heart, heterotaxy syndromes, ventricular inversion)

**CHD can be repaired or unrepaired where not specified*

ASD = atrial septal defect; AV = atrioventricular; AVSD = atrioventricular septal defect; CHD = congenital heart disease; HTAD = heritable thoracic aortic disease; LV = left ventricle/ventricular; PA = pulmonary artery; PAP = pulmonary artery pressure; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

2 Clinical and Scientific Background

2.1 Care of Adults with Congenital Heart Defects

Today, due to medical advances in surgical, interventional, and medical treatment, in the industrialized world, up to 97% of children affected by CHD reach adulthood, resulting in approximately 50 million adults with CHD (ACHD) worldwide (14), including 1.2 - 2.7 million ACHD throughout Europe (7), and about 330,000 in Germany (15). They account for over two-thirds of the current CHD population in Western countries (16). Of all ACHD, about 45% have moderate to severe heart defects (3).

Figure 1a depicts the rise in prevalence of CHD at birth from 1930 until today. This trend will continue and, as data from the United States indicate, the number of ACHD will increase steadily beyond the year 2060 (*Figure 1b*) (17, 18). In Germany, this number could potentially increase disproportionately due to a relatively high proportion of immigrants, particularly if they derive from countries with high consanguinity. However, no reliable data are available on this at present.

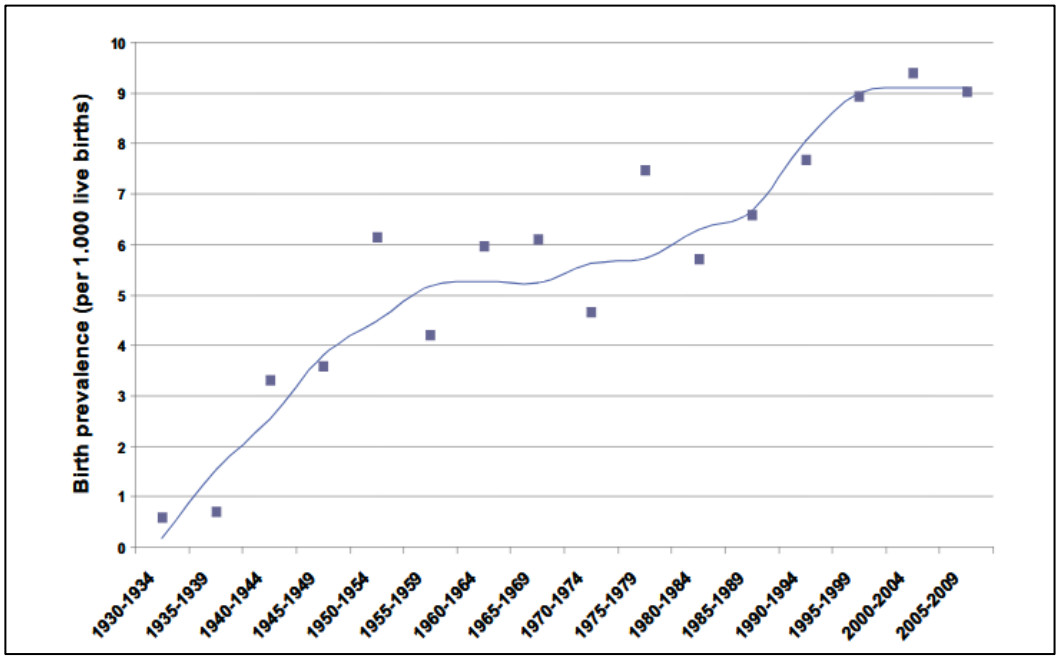


Figure 1a: *Birth prevalence of congenital heart disease from 1930 until today*, from (10)

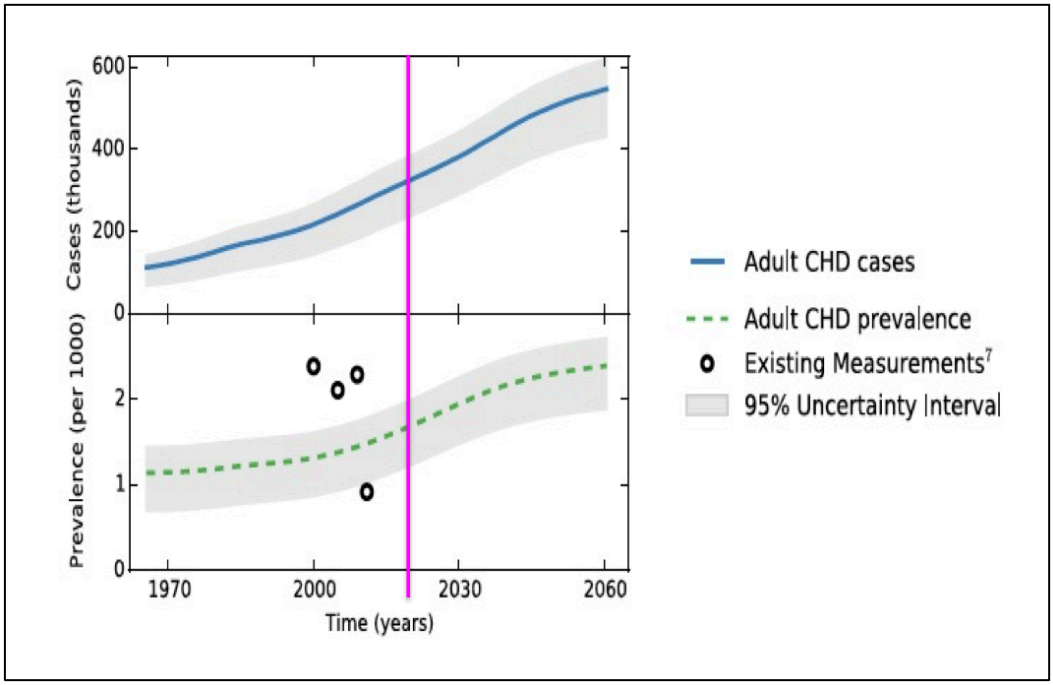


Figure 1b: *Predicted plateauing of prevalence of adults with congenital heart disease in 2050,* from (17) *(In 2050 there will be an estimated 510,000 ACHD and their prevalence will begin to plateau. Estimated number of adults (ages 20 - 64 years) with recalled CHD (blue solid line). Prevalence of recalled CHD in adults (per 1000) (green dotted line), 95 % uncertainty intervals (shaded in grey), from 1965 to 2060. Previous estimates of ACHD prevalence are marked with circles for comparison) ACHD, adults with congenital heart disease; CHD, congenital heart disease.*

Unfortunately, a complete “correction” of CHD is rarely possible, and therefore the term “repair” is used rather than “correction” (19). Consequently, the majority of ACHD are chronically ill from residua, sequelae, and complications as well as cardiac or non-cardiac comorbidities, which all may have negative effects on morbidity and mortality (20). CHD residua are caused by preexisting, heart defect-specific anatomical or hemodynamic abnormalities and do not result from any specific intervention (21, 22). By contrast, CHD sequelae result from alterations or disorders at the time of treatment. Ultimately, residua, sequelae, and complications may result in heart failure, cardiac arrhythmias, pulmonary (arterial) hypertension, infective endocarditis, aortopathies, and other conditions (23, 24).

In addition, cardiac or non-cardiac comorbidities may have a negative influence on the course of the CHD (25). Such acquired comorbidities include coronary artery disease, valvular heart disease, arterial hypertension, metabolic disorders (e.g., metabolic syndrome, hyperlipidemia, or diabetes mellitus), cerebrovascular disease, and psychiatric disorders, such as post-traumatic stress, depression, and anxiety disorders (26-28). Moreover, the presence of an underlying hereditary disease (e.g. Marfan syndrome, Ehlers-Danlos syndrome, Turner syndrome, Fabry's disease) must be taken into account (22).

For all these reasons, lifelong, specialized and interdisciplinary medical followup is of particular importance for the prevention or reduction of complications in ACHD (29, 30). ACHD patients need support and advice not only in medical and cardiac matters, but also in other areas of life, especially regarding insurance, retirement, disability, education, ability to work, resilience in everyday life, exercise, obtaining a driver's license, fitness to fly, and, often, pregnancy and genetics (31). However, it is important to keep in mind that both counseling and treatment of ACHD differ significantly from those of acquired heart disease. These consultations are difficult for treating physicians, because despite all the progress in the field of ACHD, there are still considerable information deficits. Among other issues, this relates to sex/gender differences, aortopathies, and rehabilitation measures that may influence management decisions, healthcare outcomes, and prognosis for chronically ill adult CHD patients (*Figure 2*).

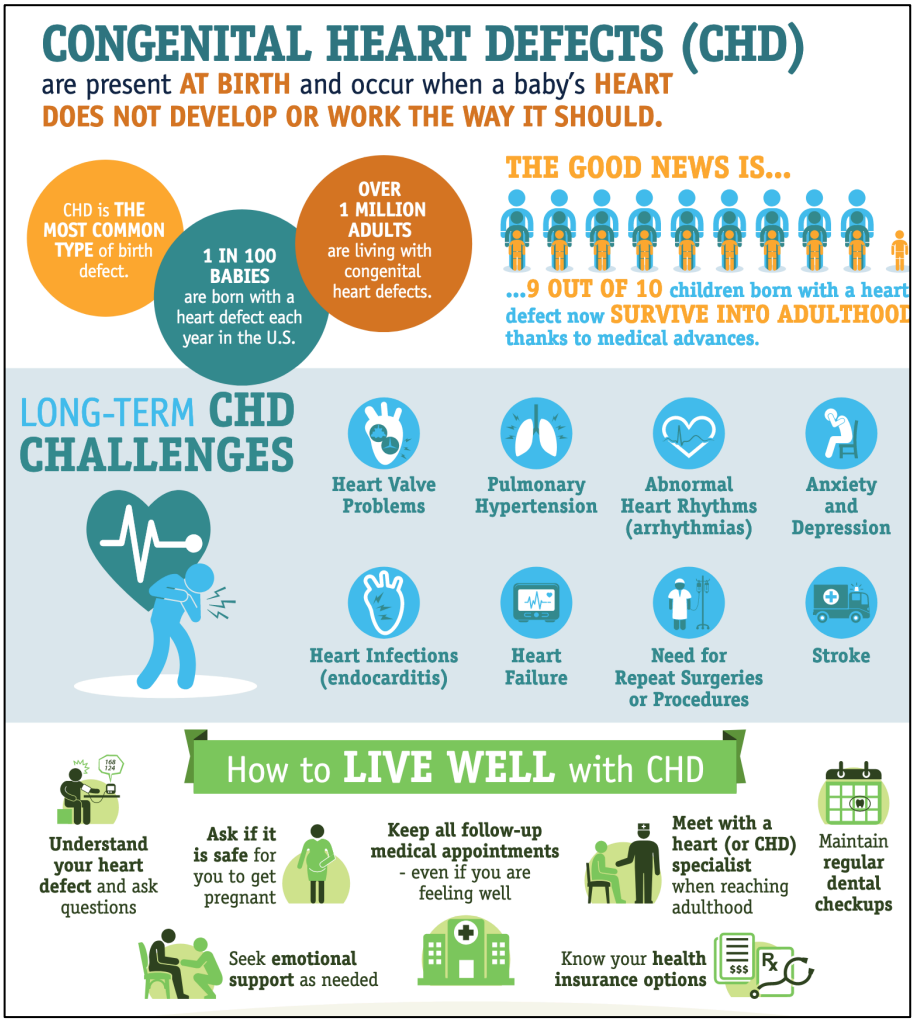


Figure 2: *Living with congenital heart disease, patient information* from: URL: https://cardiosmart.org

This dissertation will focus on sex/gender differences, aortopathies, and rehabilitation measures in ACHD. These areas have received little attention, although they appear to be essential for adequate, modern long-term care of affected patients.

2.2 Healthcare of Adults with Congenital Heart Defects in Germany

Following Joseph K. Perloff's pioneering example in Los Angeles, the need for nationwide ACHD care was addressed in Germany a few decades ago. A nationwide network of certified hospitals and medical centers, as well as clinical practices specializing in the care of ACHD, was established (27, 32-34). In order to ensure adequate care for ACHD, a three-stage care model has been developed for Germany (*Figure 3*) (27, 32).

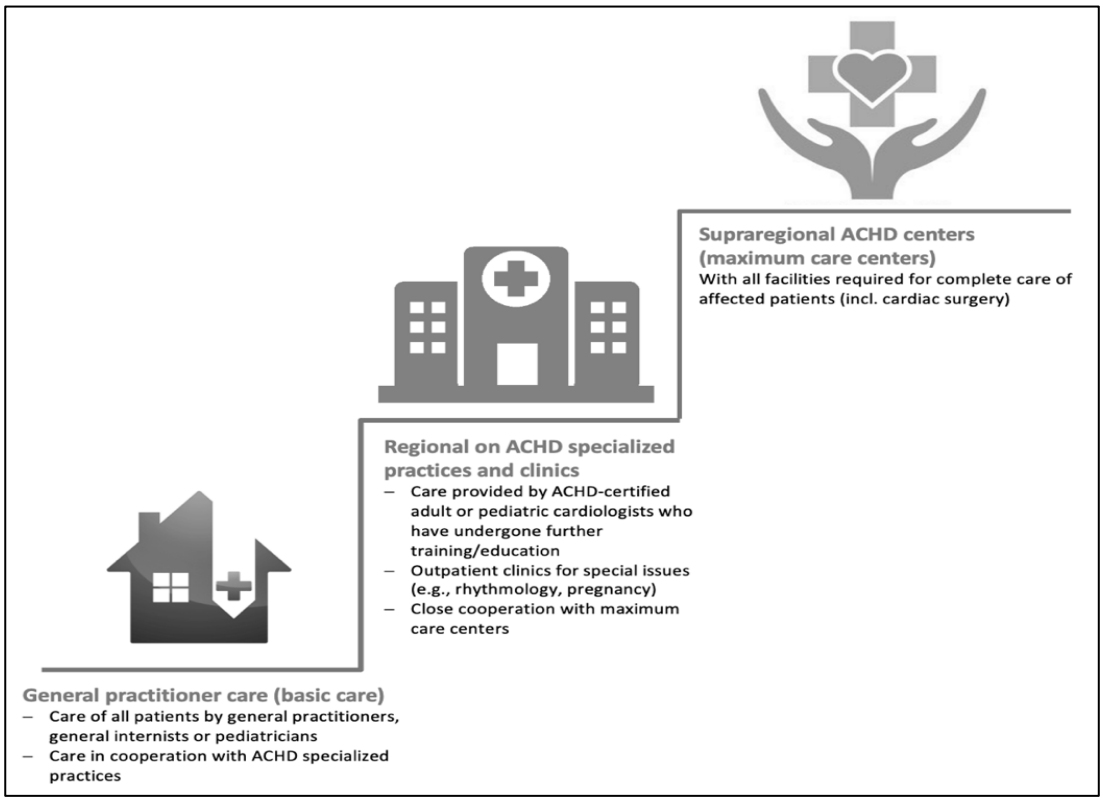


Figure 3: *Three levels of ACHD care in Germany,* from (22)

Within this system, basic medical care is provided by primary care physicians (PCPs), encompassing general practitioners, family doctors, internists, and pediatricians participating in general medical care. By referring patients to ACHD-specialized institutions, these physicians play a central role in CHD care. The second level of care includes, at present, 11 regional ACHD practices and hospitals, in which resident ACHD-certified adult or pediatric cardiologists offer ACHD care as a close-to-home treatment. A total of about 350 cardiologists and pediatric cardiologists have been accredited by medical professional societies as ACHD specialists in Germany (*Figure 4a*). The third level currently includes 20 national ACHD centers for tertiary care (*Figure 4b*), which also provide cardiac surgery and have specialized outpatient

departments (e.g. for pulmonary hypertension, cardiac arrhythmias, pregnancy, Marfan syndrome, Fabry disease, and genetic counselling) (3, 24, 27, 32, 35, 36).

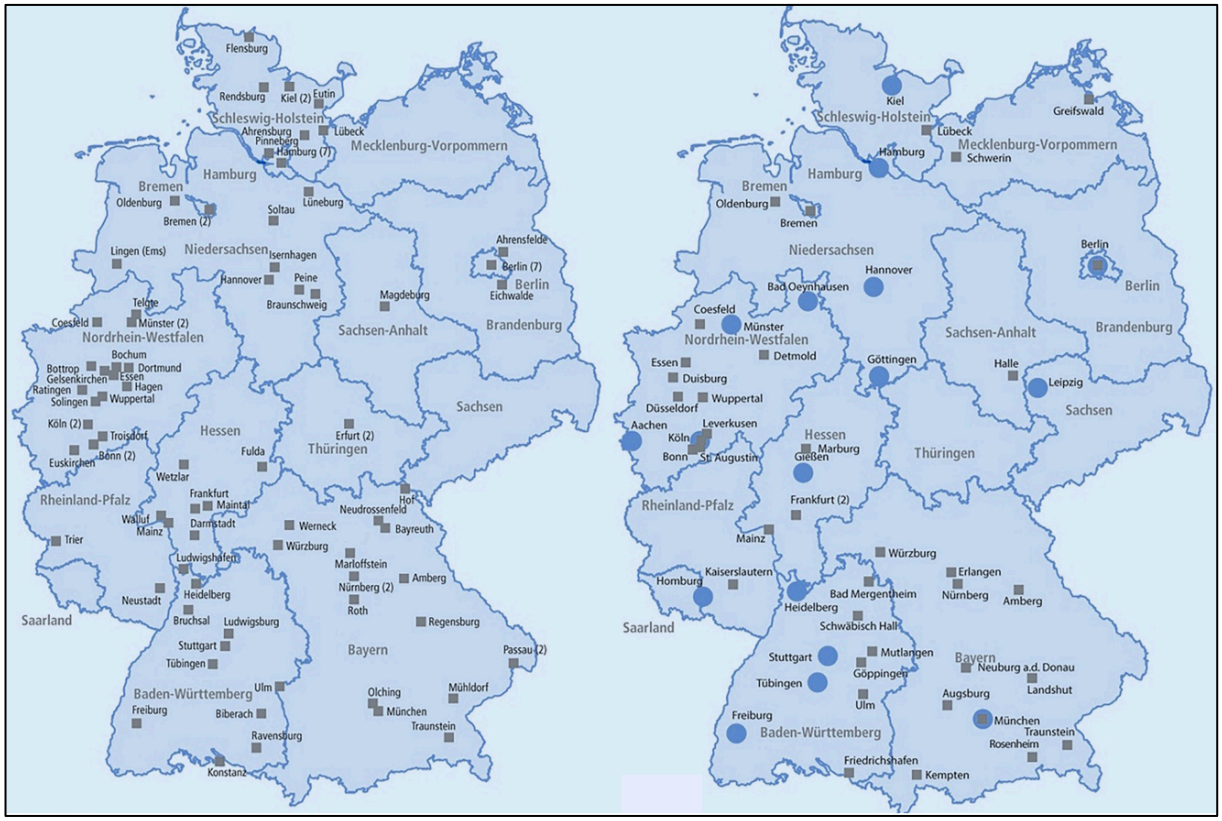


Figure 4a: *ACHD-certified adult or pediatric cardiologists (15)* ***Figure 4b****:* National ACHD centers for tertiary care (15)

Unfortunately, despite these nationwide existing ACHD-care structures, an estimated 200,000 ACHD living in Germany are not in specialized follow-up (22, 37). As current data indicate, only 21,000 ACHD are linked to one of the certified tertiary care centers for ACHD. The actual number of ACHD seen by ACHD-certified physicians in private practice is largely unknown (15). The reason for this remains speculative. ACHD themselves often neglect the need for cardiologic follow-up and do not regularly consult physicians or ACHD specialists, resulting in high loss-to-follow-up rates. This is true not only in Germany, but also in various other countries as well (38-40). Recent evidence also suggests that patients prefer to remain in the care of their PCPs, despite the availability of congenital heart specialists. In Canada, for example, 79% of ACHD with complex CHD were in contact only with their PCPs and 61% of all CHD patients have not undergone a cardiological follow-up after the age of 18 (39).

In Germany in particular, the core problem is the lack of usage of appropriate centers due to a lack of awareness, by both PCPs and the patients themselves, of the fact that ACHD are

chronically ill (22, 35, 37). They tend to ignore the reality that ACHD, even when treated surgically or interventionally, are not cured but palliated, or at best, repaired, and almost always in need of lifelong follow-up (19, 22, 27). This also applies to affected individuals who subjectively feel well and have good exercise tolerance.

This care deficit is clearly evident from recent data from a large nationwide study clarifying the care situation of ACHD. In the so-called “VEmaH-study” (German acronym for "Care situation of adults with congenital heart defects"), the current state of care for ACHD is explored both from the perspective of affected patients and from the view of their PCPs (35, 37, 41). Recent findings show that neither primary care physicians nor the patients themselves are appropriately aware of the existing ACHD care structures in Germany (35, 37). Of the nearly 800 PCPs surveyed, up to 84% reported that they treat ACHD of all age groups for both non-cardiac and cardiac issues. More than 50% of the PCPs even managed patients with moderate or severe CHD, and their counseling and treatment covered almost all typical residua and sequelae, despite the fact that these physicians are not experienced or specifically trained in CHD or ACHD care. A large proportion of surveyed physicians were even unaware of the existence of certified specialists, centers, or patient organizations, which are quite important. Only 24% of PCPs reported having ever involved an ACHD specialist in treatment decisions (35).

From the patients' perspective, the situation is similar. Of more than 4,000 participating ACHD in the survey, 88% confirmed that for any general health problems and also for cardiac problems related to the CHD, they first consulted their PCPs. At the same time, they affirmed their great need for medical advice regarding physical performance, well-being, activities of daily living, life insurance, retirement, and family planning; advice that ACHD specialists have been specifically trained to give. Yet, nearly half of the affected patients (46%) were unaware of the existence of certified ACHD specialists or centers (37). Important results of the "VEmaH-study" were also recently confirmed in the large health insurance data-based, "OptAHF" study. Diller et al. (42) concluded that of the more than 24,000 ACHD included, 50% did not receive regular cardiological care. In addition, study data showed that regular dedicated cardiological followup was associated with better survival and lower complication rates when compared with care by a PCP alone. Overall, these data suggest serious deficits in care, which have a negative impact because there is excess morbidity or mortality in ACHD not managed by specialists (16, 35, 43).

2.3 Gender and Sex Differences in Adults with Congenital Heart Defects

The term biological “sex” refers to all biological, anatomical, and physiological differences between men and women that are determined by genetic factors and hormones. A counterpart to biological sex, referred to as “gender”, is the social or cultural role of male/female identity. Gender has been shown to affect manifestation, epidemiology, and pathophysiology of many widespread diseases, as well as approaches to healthcare (44).

Despite the separation of sex and gender, both dimensions influence each other and can impact the gender-specific occurrence of a disease, its subjective perception, or even its severity and course (45). Until today, despite well-known physiological differences, clinical education and research is mainly oriented towards the male sex, or at best considered gender-neutral. For a long time, possible bias effects (“gender bias”) were not considered. However, modern medicine has recognized these deficiencies and is endeavoring to increasingly observe sex- and gender-specific differences; in particular, attempting to distinguish between the biological ("sex") and the socio-cultural ("gender") dimensions.

With regard to heart disease, there are relevant gender differences in women. They are at higher risk of developing certain types of heart disease and/or develop different cardiac symptoms from men (44). Nevertheless, even current guidelines propose therapies that were based on data from men and simply extrapolated to women (46, 47). Despite this, women continue to be underrepresented in cardiovascular clinical trials. Therefore, initiatives have been taken to include women to a greater extent. However, barriers to the enrollment and retention of women in clinical trials still exist. For example, women of childbearing age and pregnant women are often excluded from clinical research, as they represent a population that is diverse in terms of hormonal status and several other factors, introducing potential variability into trials (46, 47).

It is also of paramount importance that women with heart failure are at higher risk for adverse drug reactions than men, and adverse reactions are generally more severe in them. In addition, it has been noted that women with heart failure may require lower drug doses than their male counterparts (46). Beyond this, women are more reluctant than men to participate in clinical trials and, moreover, fewer women are treated by specialists who recruit for clinical trials (46, 47). Just recently, van Diemen et al. (46) gave recommendations to improve the representation of women towards the goal of sex- and gender-balanced cardiovascular clinical trials (see *Figure 5*).

Figure 5: *Recommendations for sex- and gender-balanced (cardiovascular) medical trials*, from (46)

Furthermore, Cho et al. (47) identify and describe the problems responsible for low recruitment and involvement of women from the perspectives of patients, clinicians, research teams, and study design, and provide recommendations for improving current patient enrollment (see *Figure 6*). For CHD, and especially in the field of ACHD, the status of gender-sensitive research is even more inadequate, and further research activities are needed. Although some smaller studies (4, 12, 48) show sex/gender-specific differences in (A)CHD, later treatment hardly addresses possible differences between men and women. Most studies focus on different incidence rates (preponderances) of CHD dependent on biological sex. However, results differ widely according to geographic region, race, and ethnicity (49).

Overall, male patients tend to have more complex/severe CHD (50) and show a higher preponderance of diseases with aortic involvement, such as aortic valve stenosis (AS), coarctation of the aorta (CoA), tetralogy of Fallot (TOF) or double outlet right ventricle (DORV) (7, 51). In female patients, a higher incidence (male/female ratio: 0.75) (52) of simple shunt defects (ASD, VSD, AVSD) were observed in recent years (53). No clear explanation exists for these sex-associated imbalances. In light of this, an effect of sex on the natural course of CHD cannot be disregarded (51).

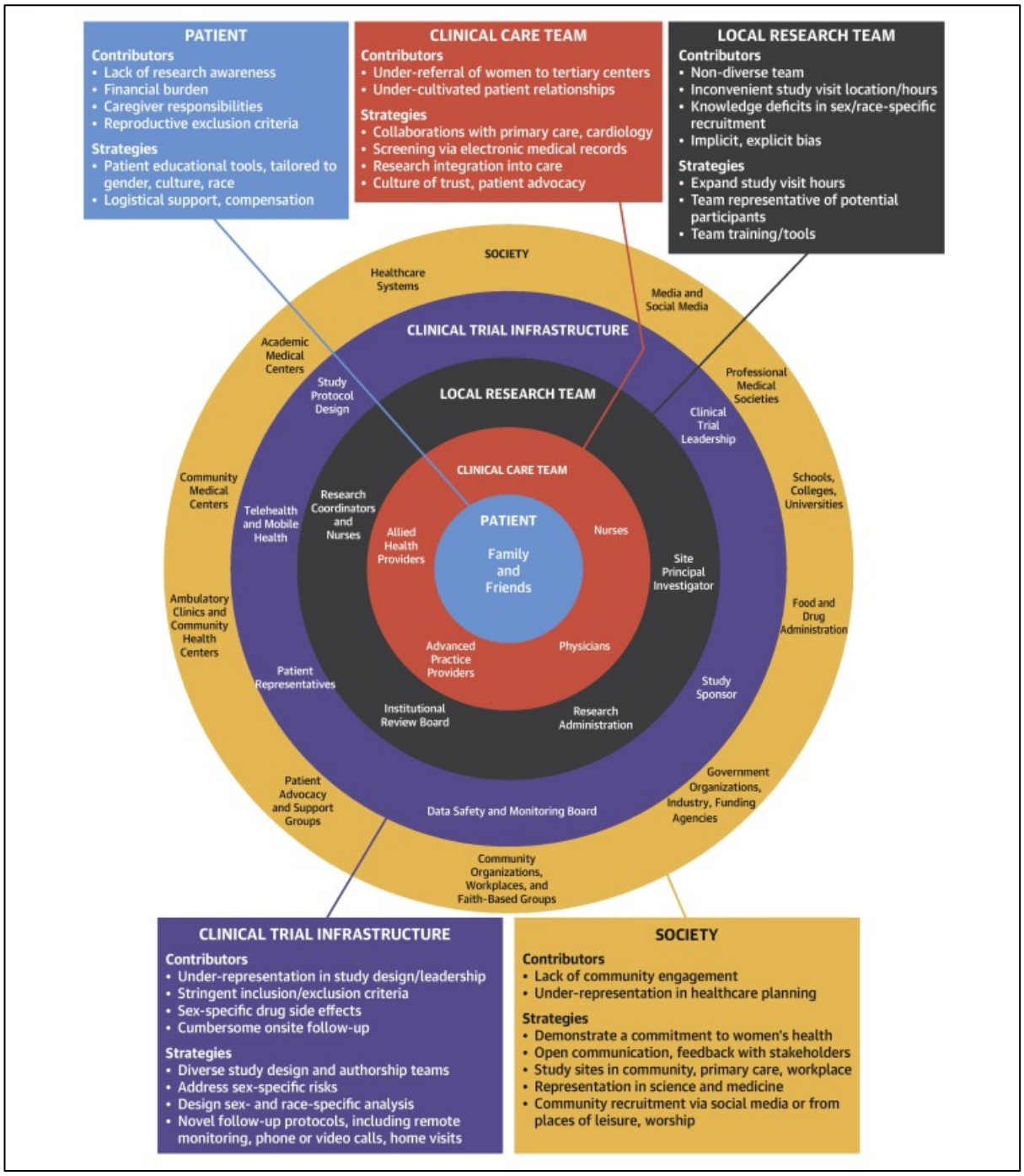
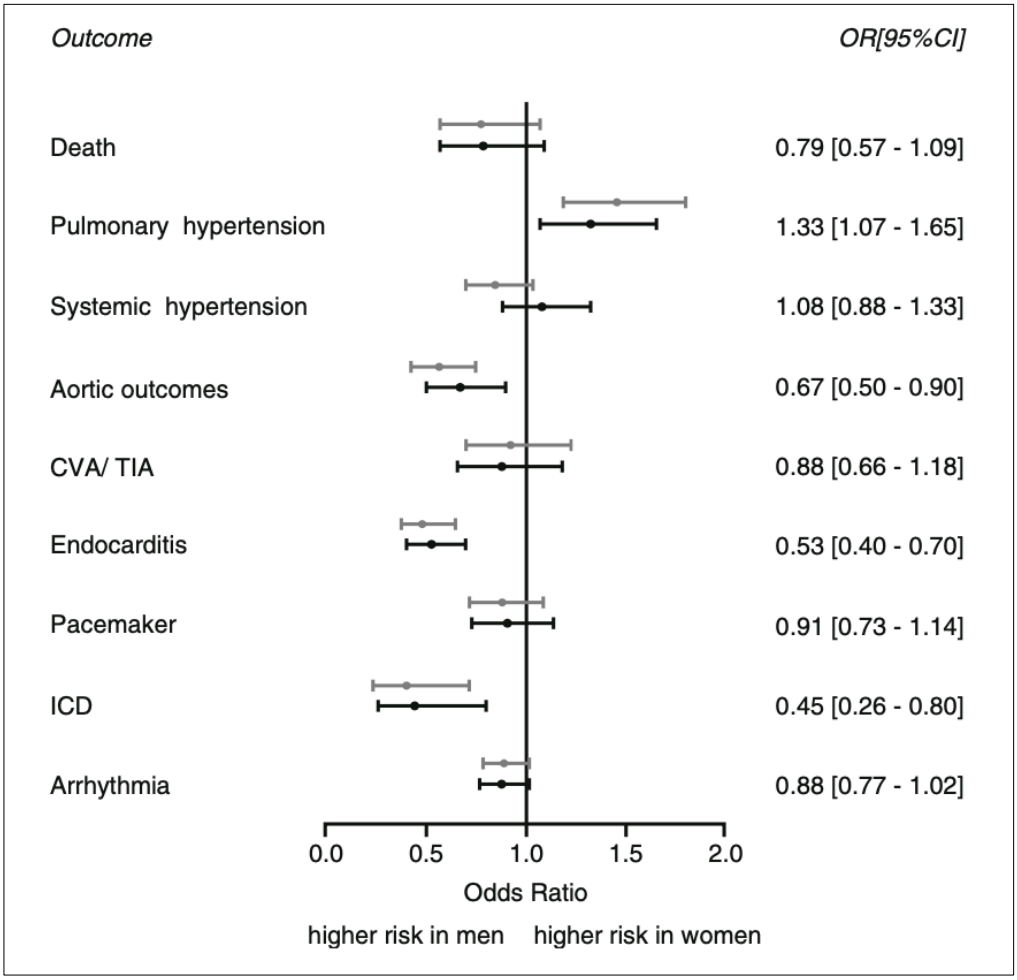


Figure 6: *Contributors and strategies to improve women´s participation in research*, from (47)

In addition, sex differences in comorbidities and prognosis have not yet been sufficiently explored in CHD, but may be of particular relevance in the long term (51). Although prevalence data are still lacking, the female predisposition to pulmonary hypertension (PH) in general and its relation to estrogen is well known (51, 54, 55). Current registry data from the Dutch CONCOR registry report that women have a 33% higher risk for developing PH (55). Data on PH in ACHD are scarce but show the same tendency, e.g., In the COMPERA registry (56, 57).

Figure 7 summarizes sex-specific odds ratios regarding common complications and comorbidities in ACHD.



**CVA, cerebrovascular accident; ICD, implantable cardioverter defibrillator, OR, odds ratio; TIA, transient ischemic attack*

Figure 7: *Common sex-dependent complications in adults with congenital heart defects,* from (50)

Also, differences in mortality and long-term survival after different interventions or operations between the sexes is controversial. Taking into account that male ACHD have a higher rate of severe CHD, the accumulated surgical risk is higher in men. Therefore, overall mortality is also higher in male patients, resulting in better long-term survival in female ACHD (50, 58, 59).

2.4 Aortic Involvement and Aortopathy in Adults with Congenital Heart Defects

The importance of aortic disease in ACHD has long been underestimated, and, although gaining in importance with age and CHD complexity, this remains an often-overlooked condition.

Aortopathy is a progressive ectasia of the proximal aortic root, the ascending aorta, or the descending aorta. It is frequently found in hereditary, syndromic disorders with aortic involvement (e.g., Marfan, Loeys-Dietz, and Ehlers-Danlos syndromes), as well as in the natural or postoperative / postinterventional course of many CHD patients (60, 61). In addition to genetically determined aortic disease, aortopathy is often associated with anomalies of the bicuspid aortic valve, aortic coarctation, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, complete transposition of the great arteries, truncus arteriosus communis, double outlet right/left ventricle, aorto-pulmonary window, or aortic arch. Also, certain patients with univentricular hearts or hypoplastic left heart syndrome after modified Fontan operation are susceptible to aortopathy (62-65). In addition, aortopathies are frequently seen after any operative treatment involving the aorta, e.g. after arterial switch operation for transposition of the great arteries, or after a Ross operation (60, 61, 66). Aortopathy is in general characterized by a degeneration of the aortic wall layer, with aortic medial degeneration, and is associated with aortic ectasia and aneurysm formation as well as aortic-ventricular interaction (66). Aortic complications, such as aneurysm, dissection, or rupture, are devastating, with a high morbidity and mortality (67). In order to prevent them, it is essential to identify high-risk patients at an early stage. If necessary, they need to be treated prophylactically or appropriate surgical or sometimes interventional treatment must be initiated in a timely manner.

Diagnostic methods for the assessment of aortopathies include various imaging techniques such as transthoracic echocardiography (TTE), magnetic resonance imaging (MRI), and computed tomography (CT) (60, 68). As long-term followup examinations should be carried out at least once a year, MRI is the preferable non-invasive method, with a high informative value and no radiation exposure (60). *Figure 8* shows examples of aortic disease in genetically determined aortic disorders as well as in other congenital heart defects. Since the prognosis of aortopathies depends decisively on the pathogenicity of the underlying disease, aetiological clarification is of outstanding importance for the prophylaxis and therapy of aortic wall changes. In order to clarify the cause of an aortopathy, genetic counselling is usually necessary in addition to the phenotyping of the patient and delineation of the family history (69). It is

important to note, however, that even a negative molecular-genetic finding does not completely exclude a genetic aortic disease such as Marfan syndrome (60, 69, 70).

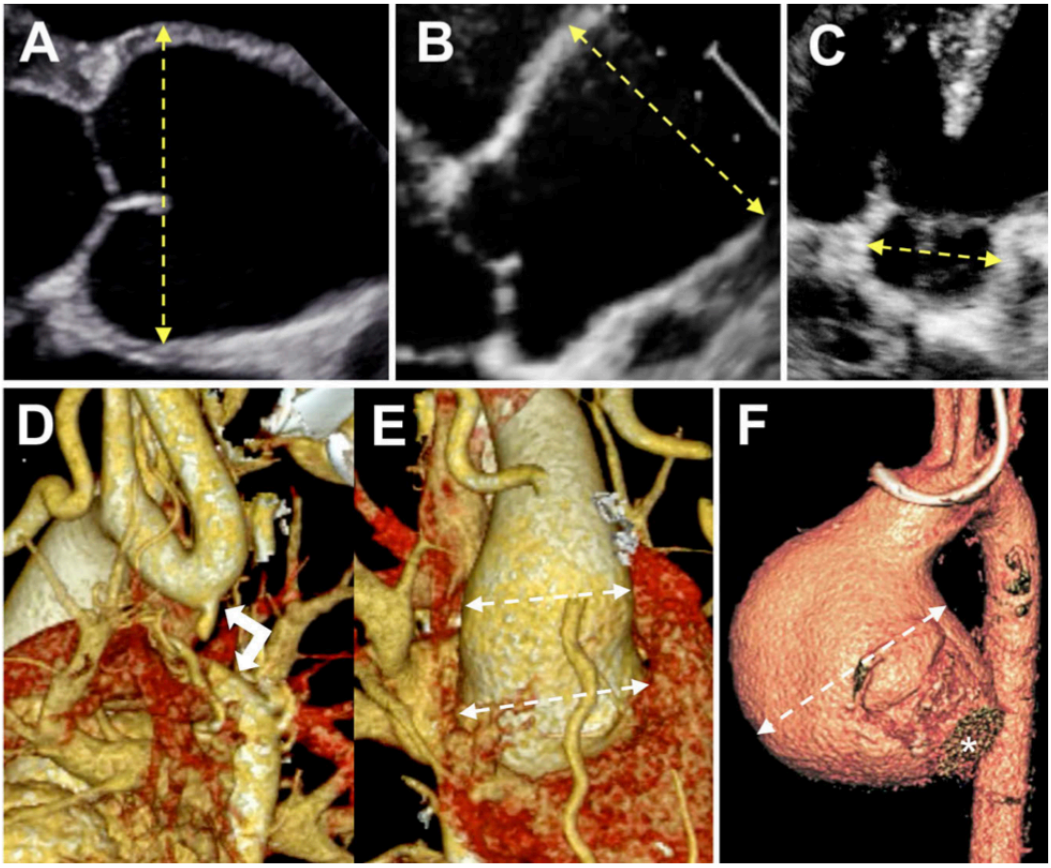


Figure 8: *Aortic aneurysm in genetically determined aortic disease and/or congenital heart defects* (with kind permission of H. Kaemmerer and M. Huntgeburth, Deutsches Herzzentrum München)

A: Aneurysm of the aortic bulb (yellow line) in a Marfan patient with the typical ("onion shape") configuration in the parasternal long axis in the TTE.

B: Aneurysm of the ascending aorta (yellow line) in a patient with bicuspid aortic valve in the parasternal long axis in the TTE. Typically, the aortic bulb and ST- junction are normal.

C: Ectatic truncus valve (yellow line) in truncus arteriosus communis with additional visualisation of a large VSD in the apical four-chamber view of the parasternal long axis in the TTE.

D and E: Aortic atresia with an atretic segment of about 1.5 cm length (arrows at the proximal and distal end) in CT. In the same patient depiction of the aneurysmatic aortic bulb and ascending aorta (white lines)

*F: 3D reconstruction (CT) of a large aneurysm of the asccending aorta (arrow), detected decades after surgical correction of a DORV with pulmonary atresia. The aortic valve plane is marked with **

**CT, computed tomography; BAV, bicuspid aortic valve; DORV, double-outlet right ventricle; TTE, transthoracic echocardiography; VSD, ventricular septal defect.*

2.5 Medical Rehabilitation Measures in Adults with Congenital Heart Defects

The term medical rehabilitation describes an interdisciplinary process in which patients with chronic diseases or patients recovering from a disease, trauma, or surgery are helped to individually regain their best possible physical and mental health and maintain it in the long term (71-73). The ultimate goal of rehabilitation measures in cardiology is to reduce cardiac morbidity and mortality (74, 75).

It is well known from patients with acquired heart disease that after an operation or a serious cardiac event, targeted cardiological rehabilitation can contribute to regaining and maintaining the best possible individual physical and mental health, as well as social integration in the long term. This can be achieved by reducing typical cardiovascular risk factors, such as obesity, arterial hypertension, and lipid disorders, and by improving physical performance, providing targeted psycho-cardiological care, and facilitating social and occupational reintegration (76).

While rehabilitation programs for patients with acquired heart disease have been extensively studied, there are no comprehensive, evidence-based data on rehabilitation for ACHD (77, 78). This is also reflected in referral rates, as ACHD are less frequently referred to a rehabilitation facility than patients with acquired heart disease (79).

Since medical rehabilitation of ACHD is often complex, rehabilitation should preferably be performed in an experienced facility with an ACHD-certified congenital cardiologist and in close cooperation with a supra-regional ACHD center (27, 32, 72, 80).

The rehabilitation process is further complicated by the fact that therapeutic goals for successful rehabilitation of ACHD are currently not appropriately defined. Only cursory guidelines or recommendations exist, and there are few concrete instructions that cover the needs of ACHD (80). In order to meet the needs of this specific patient population and to take the particularities of symptoms, residua, sequelae, and potential complications and problems into account, the near-term development of a structure for the practical implementation of rehabilitation in ACHD is critical.

3 Aims and Methods

During the course of this doctoral research study, three scientific investigations from the area of epidemiology/health services research were performed. All study results have been published in international peer-reviewed medical journals.

The study protocols were reviewed and approved by the local, participating ethics committees (studies one and two: 157/16 S; study three: 5338/12). All studies were conducted in accordance with the Declaration of Helsinki (as revised in 2013). Included patients were informed in detail about the study and gave their written consent to participate. Guidelines on good pharmacoepidemiological practice were followed. Data collection and processing were carried out in compliance with the respective federal and state data protection laws.

Data analysis was performed using SPSS 25.0 (IBM Inc., Armonk, NY, USA). All statistical evaluations of the data were pseudonymized and not linked to individual participants. Descriptive statistical methods were used for data analysis and initial characterization of the study population. Differences between the groups were checked and evaluated using the chi-square test. Student's t-test was used for comparisons between mean values. Continuous data were expressed as mean ± standard deviation, and categorical or interval-scaled variables as absolute numbers or percentages. All tests for significance were performed two-sided. A p-value <0.05 was considered significant. Since multiple answers were permitted for some questions, the number of received answers could differ from the total number of study participants included.

1. Study *(Differences in the Experiences and Perceptions of Men and Women with Congenital Heart Defects: A Call for Gender-Sensitive, Specialized, and Integrative Care)*

The aim of the first study was to elucidate patient-reported sex/gender differences concerning healthcare status, current healthcare availability, counselling needs, and quality of life (QoL) in a large cohort of ACHD, in order to provide these patients with adequate and innovative healthcare in the future. In addition to collecting clinical data, patient-reported outcome measures (PROMs) were utilized, as patients' reports of their own experiences can enable clinicians and scientists to optimize decision making and thus improve future treatment (81, 82).

This study was part of the nationwide “VemaH-study” (German acronym for "Care situation of adults with congenital heart defects"), aiming to assess the real-life healthcare status and issues of ACHD in Germany. In this cross-sectional clinical study, 3,880 patients were recruited from a tertiary care center for ACHD (Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, Technical University Munich, Germany). Data collection took place between June 2016 and October 2019.

Inclusion criteria were a confirmed diagnosis of a repaired or unrepaired (native) CHD and an age >18 years. Exclusion criteria were lack of cognitive competence to consent to research, refusal to consent, or not meeting the inclusion criteria. Patients were assigned to female and male groups according to their self-stated biological sex.

To explore sex/gender differences in ACHD, a questionnaire was specifically devised as no appropriate standardized, validated questionnaire was available. This questionnaire was developed collaboratively by the Chair of Behavioral Epidemiology at the Technical University of Dresden and the Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, Technical University Munich, Germany, tertiary care center for ACHD.

The questionnaire (see *appendix* of this doctoral dissertation) included items related to the individuals' sociodemographic status, underlying CHD, treatment status, comorbidities, general and CHD-specific medical care provision, CHD-related problems, counselling needs and desires, knowledge of CHD-specific care structures, and problems with their health care. Moreover, a validated questionnaire measuring QoL (EQ-5D-5L) from the patient's perspective via PROMs was included. The crosswalk-index-value (utility index) of the EQ-5D-5L was calculated using the German value set (83). The questionnaire was completed either in person during a stay at the hospital, online on the study homepage (http://www.vemah.info), or sent in via mail or fax (84).

2. Study *(Provision of Medical Health Care for Adults with Congenital Heart Disease associated with Aortic Involvement)*

The aim of the second study was to acquire real-world data on the medical care of aortic abnormalities in the context of a congenital or hereditary aortopathy. The health status of patients and/or the provision of health care by general practitioners and family doctors (i.e., “primary care providers”) were assessed. In this cross-sectional clinical study, 563 patients

with a congenital or hereditary aortopathy being seen at the Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, were included. Patients were consecutively included in the order that they presented at the institution and were not selected a priori. This study was part of the above-mentioned “VEmaH study”.

Inclusion criteria were a confirmed diagnosis of a native or repaired CHD and an age >18 years. Exclusion criteria were lack of cognitive competence to consent to research, refusal to consent, or not meeting the inclusion criteria. For the PROMs (socio-demographics, CHD, comorbidities, care providers for medical problems in general and CHD-related problems, individual patient needs for counselling, knowledge of specific care structures, and problems with the care situation from the patient’s perspective), the same questionnaire was used as in the first study (*Article 1*). In addition, patients’ medical records were reviewed for demographics and for both cardiac and non-cardiac diagnoses.

Patients were assigned to one of six classes of diagnosis, depending on the type of underlying CHD ((I) complex CHD; (II) disorders of the left heart/anomalies of the aortic valve or aorta; (III) disorders of the right heart/anomalies of pulmonary valve or pulmonary artery; (IV) primary left-to-right shunt lesions - either at pre-tricuspid or post-tricuspid level; (V) genetic syndromes; or (VI) other congenital/non-classifiable congenital heart anomalies; see *Table 2*). According to the underlying pathological anatomy, pathophysiology, and epidemiological data from the recent literature, ACHD were further divided into two additional groups based on aortopathy risk: “at risk for developing aortopathy and/or manifest aortopathy” or “without risk of intrinsic aortopathy”. In this context, “aortopathy” was defined either on the basis of the underlying disease with “intrinsic” pathologic aortic alterations or on the basis of the reported absolute diameter of the aortic root or the ascending aorta. “Intrinsic” pathologic aortic alterations with abnormality of vessel architecture were presumed based on data from the literature for syndromic and non-syndromic congenital or hereditary congenital anomalies (66).
In the present survey, an absolute diameter of the aortic root or the ascending aorta of >38 mm in a normal-sized adult was considered pathologic, without correcting the normal range for age, weight, sex, or body surface area. This was suitable for this survey, since the definition of a “normal aorta size” is still under discussion and robust data on aortic size in the “normal” population are missing (85), particularly in patients with CHD (41).

Table 2: *Main Diagnostic Groups and their Underlying Congenital Heart Defects*

Diagnosis-Group		Leading Congenital Heart Disease
I.	Complex CHD	Discordant atrio-ventricular or ventriculo-arterial connections (including TGA-atrial switch, TGA-arterial switch, TGA-Rastelli, CCTGA and DORV-TGA)
		Univentricular hearts (including DIV and TrA)
		Pulmonary atresia with intact ventricular septum
		Truncus arteriosus communis
		Other complex CHD (including Ebstein's anomaly and others)
II.	Disorders of the left heart/ Anomalies of the aortic valve or aorta	Bicuspid aortic valve/aortic valve anomalies
		Aortic valve stenosis (sub- and supra-valvular aortic stenosis)
		Interrupted aortic arch
		Aortic coarctation
III.	Disorders of the right heart/ Anomalies of pulmonary valve or pulmonary artery	Tetralogy of Fallot
		Double outlet right ventricle of Fallot type
		Pulmonary atresia with ventricular septal defect
		Pulmonary valve anomaly and pulmonary artery anomaly
IV.	Primary left-to-right shunt lesions - either at pre-tricuspid or post-tricuspid level	Atrial septal defect
		Persistent foramen ovale
		Partial atrio-ventricular septal defect
		Partial anomalous pulmonary venous return
		Total anomalous pulmonary venous return
		Ventricular septal defect
		Complete atrio-ventricular septal defect
		Patent ductus arteriosus
V.	Genetic syndromes	Marfan- or Loeys-Dietz syndrome
		Aortic aneurysm of unknown origin
VI.	Other congenital/ Non-classifiable congenital heart anomalies	Congenital cardiomyopathy
		Congenital valve anomaly
		Congenital other

** CCTGA, congenitally corrected transposition of the great arteries; CHD, Congenital heart disease; DIV, Double inlet ventricle; DORV-TGA, Double outlet right ventricle - transposition of the great arteries; TGA, Transposition of the great arteries; TrA Tricuspid atresia.*

3. Study *(Lessons from Short- and Medium-term Outcomes of Medical Rehabilitation in Adults with Congenital Heart Disease)*

In the third study, comprehensive data on the course of medical rehabilitation were acquired in a large cohort of ACHD after surgical or interventional treatment. The aim was to obtain for the first time detailed data on the specific needs of ACHD requiring medical rehabilitation and to develop, on the basis of the acquired data, a concept for rehabilitation measures for ACHD. This retrospective cohort study on the medical care and rehabilitation of ACHD was initiated by the Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, in cooperation with a specialized rehabilitation clinic, Klinik Höhenried, Bernried, Germany. Inclusion criteria were the presence of a CHD, a completed rehabilitation measure, medical follow-up, and written consent to participate in the study. Exclusion criteria were lack of cognitive competence to consent to participate in the research and the refusal to consent.

The medical records for the inpatient stay and follow-up care were analyzed. Based on each patient's medical history and the clinical assessment of the treating physicians, all patients were classified into one of four functional classes, based on the classification of Perloff (86). This classification was developed specifically for ACHD and is similar to the NYHA classification of heart failure. Since the symptoms of functional classes I and II as well as III and IV are fluid, the patients were grouped into two joint functional classes, I/II or III/IV, for statistical analysis. Furthermore, on the basis of the underlying heart defect, patients were assigned to one of three disease severity classes (87).

4 Scientific Publications

4.1 Scientific Publication 1 *(published in „International Journal of Cardiology - Congenital Heart Disease“, IF pending – scoped 4 to 5)*

Differences in the Experiences and Perceptions of Men and Women with Congenital Heart Defects: A Call for Gender-Sensitive, Specialized, And Integrative Care

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(II) Administrative support: All authors
(III) Provision of study materials or patients: **SF**, RN, HK
(IV) Collection and assembly of data: **SF**, LP, RN
(V) Data analysis and interpretation: **SF**
(VI) Initial manuscript writing: **SF**
(VII) Final approval of manuscript: All authors.

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Differences in the experiences and perceptions of men and women with congenital heart defects: A call for gender-sensitive, specialized, and integrative care

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ABSTRACT

Background: Although there is sufficient evidence that sex-/gender-based differences can influence treatment decisions and healthcare for adults with congenital heart disease (ACHD), there are major research shortfalls in this regard. The aim of this study was to assess these in a large ACHD cohort.
Methods: In this cross-sectional study, patient-reported outcome measures from a questionnaire completed by 3880 ACHD (53.6% female; 41.9 ± 17.1 years) were used to assess gender-related differences concerning underlying CHD condition, comorbidities, health care details, individual counselling needs, and quality of life (QoL).
Results: Significant differences observed included a female predominance in tetralogy of Fallot, atrial septal defects, and persistent ductus arteriosus, and a male predominance in aortic valve stenosis/insufficiency and transposition of the great arteries. The prevalence of coronary artery disease was significantly higher in men, while women reported a higher prevalence of pulmonary hypertension, arrhythmias, neurologic restrictions, and overall comorbidities. Men consulted their primary care physician more often if a CHD-related medical problem was suspected. A total of 2194 patients (54.4% female) stated that they had never been referred to an institution specialized in CHD. Both sexes had a high counselling demand, but there were significant differences between male and female participants. In terms of QoL, female participants reported greater impairments, especially in everyday activities, more pain/physical complaints, and more anxiety/depression.
Conclusion: Both specialists and primary care physicians (PCPs) require an understanding of the importance of gender-based differences in ACHD, since, for the majority of ACHD, PCPs are the first contact persons for medical issues.

1. Introduction

Every year, approximately 1.5 million children worldwide are born with congenital heart defects (CHD). Due to medical advances in pharmaceutical, interventional, and surgical treatment, more than 95% of the affected children now reach adulthood [1]. With a prevalence of 0.3% in a world population of approximately 4.4 billion adults, a total number of 13 million adult CHD survivors can be estimated globally [2]. Of these, the approximate number of adults with congenital heart disease (ACHD) is 1.4 million in the US, 2.3 million in the European Union, and 330,000

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in Germany [2–5]. In contrast to acquired heart disease or other chronic diseases, there is a lack of knowledge in CHD and especially in ACHD regarding biological sex- and gender-related differences. Biological sex refers to biological, anatomical, and physiological differences between men and women that are determined by genetic factors and hormones. A counterpart to biological sex is the social or cultural roles of male or female identity, and this is referred to as gender. Gender has been shown to affect manifestation, epidemiology, and pathophysiology of many widespread diseases, as well as approaches to healthcare [6]. Here, we express differences between men and women as gender differences unless they have clear causal roots in biological sex. Despite all research efforts, the underlying pathomechanisms of CHD, and reasons for gender-specific differences in distribution and outcomes, are largely unknown [7]. In congenital cardiology, more attention needs to be paid to gender-related aspects of social behavior and the patient's role in society [8]. Patient surveys and the patient-reported outcome measures (PROMs) they yield are therefore essential.

The aim of the present study was to elucidate patient-reported gender differences concerning the healthcare status, current healthcare supply, counselling needs, and quality of life (QoL) in a large cohort of ACHD, in order to provide these patients with adequate and innovative healthcare in the future.

2. Patients and methods

2.1. Study cohort

In this cross-sectional clinical study, 3880 patients were recruited from a tertiary care center for ACHD (Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, Technical University Munich, Germany). The current study was part of the nationwide "VemaH study", which aims to assess the real-life health care status and issues of ACHD in Germany. Data collection took place between June 2016 and October 2019.

The survey was approved by the institutional review boards of the Technical University Munich (157/16 S), and written informed consent was obtained from all participating patients before the start of documentation. Participation or non-participation in the study had no influence on the medical care of the patients. Guidelines on good pharmacoepidemiologic practice and data protection guidelines were followed.

2.2. Patient inclusion and classification

Inclusion criteria for the present study were a confirmed diagnosis of CHD, whether or not the heart defect was native or repaired, and an age >18 years. Exclusion criteria were lack of cognitive competence to consent to research, refusal to consent, or not meeting the inclusion criteria. Patients were assigned to female and male groups according to their self-stated gender.

2.3. Questionnaire

In order to explore gender differences in ACHD, it was not possible to use a standardized and validated questionnaire. For this purpose, a questionnaire was specifically devised in cooperation with the Chair of Behavioral Epidemiology at the Technical University of Dresden and the Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, Technical University Munich, Germany, tertiary care center for ACHD. This questionnaire included items related to the individuals' sociodemographic status, underlying CHD, treatment status, comorbidities, general and CHD-specific medical care provision, CHD-related problems, demands for counselling, knowledge of CHD-specific care structures, and problems with their health care. Moreover, a validated questionnaire measuring quality of life (EQ-5D-5L) from the patient's perspective via PROMs was included. The questionnaire was completed either in person during a stay at the hospital, online on the study homepage (http://www.vemah.info), or sent in via mail or fax.

2.4. Statistical analysis

Data analysis was performed using SPSS 25.0 (IBM Inc., Armonk, NY, USA). All statistical evaluations of the data were pseudonymized and not linked to individual participants. Descriptive statistical methods were used for data analysis and initial characterization of the study population. Differences between the groups were checked and evaluated using the chi-square test. Student's t-test was used for comparisons between mean values. Continuous data were expressed as mean ± standard deviation, and categorical or interval-scaled variables as absolute numbers or percentages. The crosswalk-index-value (utility index) of the EQ-5D-5L was calculated using the German value set [9]. All tests for significance were performed two-sided. A p-value <.05 was considered significant. Since multiple answers were permitted for some questions, the number of received answers may differ from the total number of study participants included.

3. Results

A total of 3880 patients, aged 41.9 ± 17.1 [range: 18–97] years, were included in this cross-sectional clinical study. The mean age of the 2079 female participants, 41.6 ± 16.8 [range: 18–97] years, did not differ significantly from that of the 1801 male participants (42.1 ± 17.5 [18–91] years).

3.1. Self-reported CHD diagnosis

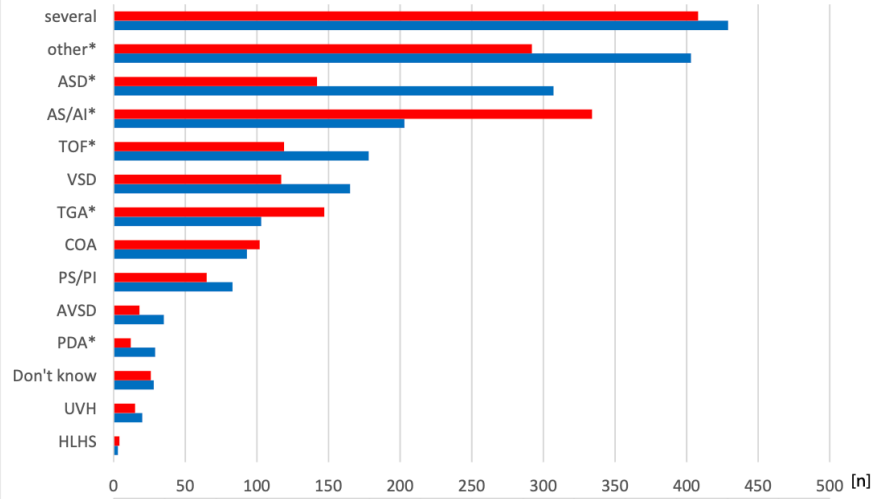
Almost all types of CHD were represented in the study cohort. Fig. 1 shows the sex ratio (male/female) in relation to the patient-reported underlying CHD. Among these, transposition of the great arteries (OR: 0.61; p = .001), aortic valve disease (OR: 0.53; p = .001), and coarctation of the aorta (OR: 0.79; p = .091) were more often reported by men than by women. Female participants reported significantly more tetralogy of Fallot (OR: 1.30; p = .022), persistent ductus arteriosus (OR: 2.09; p = .0.027), atrial septal defects (OR: 1.87; p = .001), and other or unspecified CHD (OR: 1.20; p = .010) as their main defect. Atrioventricular septal defects (OR: 1.68), ventricular septal defects (OR: 1.22), and pulmonary valve stenosis/insufficiency (OR: 1.11) were reported more often by women than by men, but these differences were not statistically significant.

3.2. Self-reported comorbidities and degree of disability

The overall prevalence of comorbidities was higher in women than in men (62.5% vs. 46.6%, p < .001). With the exception of coronary artery disease, coagulation abnormalities, and haematologic diseases, female participants reported more disorders or limitations in all categories (see Table 1). Significant differences were found with regard to arrhythmias (OR: 1.34; p = .001), neurological restrictions (OR: 1.42; p = .031), pulmonary hypertension (OR: 1.79; p = .001), and coronary artery disease (OR: 0.71; p = .032). The degree of disability differed significantly between both sexes (p = .016), with male participants reporting a higher degree of disability (37.9 ± 31.6) than female participants (34.9 ± 33.1).

3.3. Patient-reported healthcare outcomes

In Germany, basic medical care is provided by primary care physicians (PCPs), a generic term for all doctors who participate in general medical care. For both male and female ACHD, the primary medical care provider for "general, CHD-independent, medical issues" was a PCP (97.0% vs. 96.9%, p > .05). Among these ACHD, 91.6% of the women and 90.5% of the men reported that their PCP was aware of their CHD. The remaining 8.4% and 9.5% (female and male participants,



	HLHS	UVH	Don't know	PDA*	AVSD	PS/PI	COA	TGA*	VSD	TOF*	AS/AI*	ASD*	other*	several
Males	4	15	26	12	18	65	102	147	117	119	334	142	292	408
Females	3	20	28	29	35	83	93	103	165	178	203	307	403	429

Fig. 1. Sex distribution per defect: Patient-reported diagnosis of their primary congenital heart defects, by sex (in absolute numbers). n = absolute number, HLHS= Hypoplastic left heart syndrome, UVH= Univentricular heart, PDA= Persistent ductus arteriosus, AVSD = Atrioventricular septal defect, PS/PI= Pulmonary valve stenosis/insufficiency, COA= Coarctation of the aorta, TGA = Transposition of the great arteries, VSD= Ventrical septal defect, TOF = Tetralogy of Fallot, AS/AI = Aortic valve stenosis/insufficiency, ASD = Atrial septal defect, Other = other CHD than listed, Several = more than one CHD; *, statistically significant ($p \leq .05$).

Table 1
Patient-reported cardiac and non-cardiac comorbidities, overall and by sex (relative and absolute frequencies).

Patient-reported comorbidities	Overall % (N)	Women % (n)	Men % (n)	p-value
Arrhythmias	29.4% (1141)	33.4% (694)	24.8% (447)	**0.001****
Heart failure	12.8% (495)	13.3% (277)	12.1% (218)	0.270
Psychological restrictions	7.6% (296)	8.3% (173)	6.8% (123)	0.081
Coagulation abnormalities	6.3% (244)	6.2% (128)	6.4% (116)	0.716
Neurologic restrictions	3.9% (153)	4.6% (95)	3.2% (58)	**0.031***
Coronary artery disease	3.8% (149)	3.2% (67)	4.6% (82)	**0.032***
Pulmonary hypertension	3.7% (144)	4.7% (97)	2.6% (47)	**0.001****
Thrombosis	3.6% (141)	4.1% (85)	3.1% (56)	0.104
Haematologic disorders	2.7% (105)	2.6% (55)	2.8% (50)	0.802
"I don't know"	12.5% (484)	12.0% (250)	13.0% (234)	0.363
Overall prevalence	55.1% (2138)	62.5% (1299)	46.6% (839)	**0.001****

N, total number in overall population, n, absolute number within group; *, statistically significant ($p \leq .05$); **, statistically highly significant ($p \leq .001$).

respectively) could not provide any information on this or they stated that they did not know whether their PCP was aware of their CHD. These differences between the sexes were not significant ($p = .497$). When asked about the first contact person for "CHD-specific health problems", 53.6% ($n = 2079$) of the patients stated that it was their PCP, even for heart problems or cardiac related issues. The remaining 46.4% ($n = 1801$) consulted a doctor with a different specialization, including cardiology. These findings differed significantly between the genders ($p = .001$), as men were more likely to consult their PCP when CHD-specific problems occurred (57.4% of male vs. 50.3% of female participants). All patients were asked about their awareness of ACHD-specialized institutions. ACHD-certified adult and pediatric cardiologists, regional dedicated ACHD practices and hospital units, as well as national tertiary care centers, were widely unknown to the majority of participants. Significant differences were found in the awareness of ACHD-certified pediatric cardiologists (26.1% for women vs. 23.2% for men, $p = .041$) and national tertiary care centers for ACHD (28.0% for women vs. 24.6% for men, $p = .016$). Remarkably, 44.7% of the female participants and 47.2% of the male participants were unaware of any ACHD-specialized institutions. More of the female participants reported being insufficiently informed about ACHD-specialized institutions (44.3%) than the male participants (40.1%) ($p = .007$). A similar difference was seen in awareness of "patient organizations for ACHD". Only 33.2% of the women and 28.0% of the men felt adequately informed of their existence ($p - .001$). Of all participants, 29.4% (29.6% female, $n - 615$; 29.1% male, $n = 524$) reported that their PCP had never referred them to a CHD specialist for cardiac problems related to their CHD. Only 5.6% (5.5% female, $n = 114$; 5.8% male, $n = 104$) had been referred to an ACHD specialist for a medical problem that could affect the CHD. Overall, 56.5% (57.4% female, $n = 1193$; 55.5% male, $n = 999$) of the respondents stated that they had never been referred to a CHD-specialized institution by their PCP. The question concerning "satisfaction in the context of medical care for your CHD" was answered on a scale of 1–6 (1 = very good; 6 = unsatisfactory). Significantly more female participants rated their medical care as worse; on average, female patients gave their care a rating of 2.12 (good), while male patients gave their care an average rating of 2.01 (good) ($p = .001$).

3.4. Specific counselling needs for ACHD

Of the 3880 patients surveyed, 1297 stated that they did not need specific counselling. Of the remaining 2583 patients, significantly fewer men indicated a need for counselling (69.1% of the women vs. 63.6% of the men, $p = .002$). The patients' reported need for counselling, separated by gender, is shown in Table 2 (multiple answers possible). Female participants reported their greatest needs for counselling with regard to pregnancy, exercise capacity, retirement/pension, and resilience in everyday life. Male participants predominantly sought advice on retirement/pension, resilience in everyday life, and health insurance. Gender-specific differences in counselling needs existed particularly for exercise capacity ($p = .001$), resilience in everyday life ($p = .002$), pension ($p = .016$), pregnancy ($p = .001$), rehabilitation measures ($p = .005$), severe

Table 2
Specific counselling needs from the patient's perspective (by sex, in absolute numbers and %).

Specific counselling need	Overall % (N)	Women % (n)	Men % (n)	p-value
Exercise capacity	35.0% (1359)	39.6% (824)	29.7% (535)	**0.001****
Retirement insurance	33.6% (1303)	35.2% (732)	31.7% (571)	0.075
Resilience in everyday life	32.6% (1263)	34.7% (722)	30.0% (541)	**0.002***
With regard to pension	31.8% (1234)	33.5% (696)	29.9% (538)	**0.016***
Pregnancy	30.0% (1164)	42.8% (889)	15.3% (275)	**0.001****
Health insurance	29.8% (1156)	29.9% (621)	29.7% (535)	0.998
Life insurance	29.1% (1130)	30.9% (643)	27.5% (496)	0.157
Rehabilitation measures	27.9% (1081)	29.8% (619)	25.7% (462)	**0.005***
With regard to severely handicapped persons	22.1% (859)	23.4% (487)	20.7% (372)	**0.042***
Education forms	21.5% (835)	22.5% (468)	20.4% (367)	0.112
Career opportunities	21.5% (834)	21.2% (440)	21.9% (394)	0.579
Genetic counselling	20.1% (780)	23.0% (478)	16.8% (302)	**0.001****
Driver's license	17.8% (689)	19.9% (413)	15.3% (276)	**0.001****
Respiratory capacity to fly	17.2% (666)	20.1% (417)	13.8% (249)	**0.001****

N = total number of cases; n = number of cases in subgroup; *, statistically significant ($p \leq .05$); ** statistically highly significant ($p \leq .001$).

disability ($p = .042$), genetic counselling ($p = .001$), driver's license ($p = .001$) and respiratory capacity to fly ($p = .001$). All listed needs were reported significantly more often by female participants.

3.5. Quality of life in ACHD

Of the study participants, a total of 3435 patients (54.1% female) completed the additional EQ-5D-5L questionnaire on quality of life (QoL) and the associated visual analogue scale (VAS). Table 3 shows the QoL of the study participants, separated by gender. The female ACHD reported a worse QoL in all five dimensions of the EQ-5D-5L questionnaire compared with their male counterparts. Significant differences were found in activities of daily life ($p = .001$), pain/discomfort ($p = .004$), and anxiety/depression ($p = .001$). Female participants also reported a worse health-related QoL as represented by the VAS (76.06 ± 19.08 vs. 76.49 ± 18.86; $p = .501$), the crosswalk index value/utility index (90.08 ± 15.89 vs. 91.45 ± 14.69; $p = .008$), and both QoL measures combined (83.28 ± 15.76 vs. 84.21 ± 14.99; $p = .501$), in comparison with male participants.

4. Discussion

Even though it is well established that gender differentially affects the manifestation, epidemiology, and pathophysiology of many diseases, as well as approaches to health care [6], prior research has only addressed gender aspects in CHD to a very limited extent. In addition, the quality, comparability, and external validity of the few available studies vary considerably [6,10–12]. The present study is the first major exploration of patient-reported, gender-specific differences in medical issues, current healthcare status, counselling needs, and QoL in a consecutively recruited cohort of ACHD. In contrast to previous studies, we did not collect clinical data. Instead, we utilized PROMs, as patients' reports of their own experience can enable clinicians and scientists to optimize decision making and thus improve future treatment [13].

Table 3
Quality of life from the patient's perspective (by sex, in absolute numbers and %).

EQ-5D-5L	Total sample		Women		Men		p-value
Dimension	N	%	n	%	n	%	
Mobility							
No problems	2814	72.5%	1503	72.3%	1311	72.8%	0.848
Slight problems	444	11.4%	244	11.7%	200	11.1%	
Moderate problems	305	7.9%	168	8.1%	137	7.6%	
Severe problems	114	2.9%	66	3.2%	48	2.7%	
Extreme problems	17	0.4%	9	0.4%	8	0.4%	
Missing response	186	4.8%	89	4.3%	97	5.4%	
Self-care							
No problems	3432	88.5%	1848	88.9%	1584	88.0%	0.872
Slight problems	138	3.6%	70	3.4%	68	3.8%	
Moderate problems	68	1.8%	36	1.7%	32	1.8%	
Severe problems	31	0.8%	18	0.9%	13	0.7%	
Extreme problems	23	0.6%	14	0.7%	9	0.5%	
Missing response	188	4.8%	93	4.5%	95	5.3%	
Activities of Daily Life							
No problems	2574	66.3%	1331	64.0%	1243	69.0%	**0.001****
Slight problems	620	16.0%	372	17.9%	248	13.8%	
Moderate problems	322	8.3%	179	8.6%	143	7.9%	
Severe problems	123	3.2%	79	3.8%	44	2.4%	
Extreme problems	42	1.1%	25	1.2%	17	0.9%	
Missing response	199	5.1%	93	4.5%	106	5.9%	
Pain/Discomfort							
No problems	2135	55.0%	1091	52.5%	1044	58.0%	**0.004***
Slight problems	925	23.8%	527	25.3%	398	22.1%	
Moderate problems	451	11.6%	260	12.5%	191	10.6%	
Severe problems	126	3.2%	71	3.4%	55	3.1%	
Extreme problems	15	0.4%	11	0.5%	4	0.2%	
Missing response	228	5.9%	119	5.7%	109	6.1%	
Anxiety/Depression							
No problems	2157	55.6%	1069	51.4%	1088	60.4%	**0.001****
Slight problems	985	25.4%	589	28.3%	396	22.0%	
Moderate problems	350	9.0%	217	10.4%	133	7.4%	
Severe problems	147	3.8%	79	3.8%	68	3.8%	
Extreme problems	30	0.8%	18	0.9%	12	0.7%	
Missing response	211	5.4%	107	5.1%	104	5.8%	

EQ-5D-5L = European Quality of Life 5 Dimensions – 5 Levels questionnaire; N = total number of cases; n = number of cases in subgroup; *,statistically significant ($p \leq .05$); ** statistically highly significant ($p \leq .001$).

4.1. Patient-reported CHD diagnosis

This survey of 3380 ACHD included almost all types and severity degrees of CHD. More women participated (n = 2079; 53.6%) than men. This seemed reasonable, as previous studies also reported an overall higher prevalence of CHD in women [14–16]. Due to the development of fetal echocardiography and the simplified possibility of abortion, a shift in severity from complex to relatively simple CHD has been observed in

recent years [10]. In previous studies, women have shown an overall higher preponderance of relatively simple CHD, compared with men [8]. We arrived at similar findings; in our study, female ACHD reported an overall higher preponderance of relatively simple CHD, compared with male ACHD. Previously reported examples of sex-associated differences in adult CHD prevalence include persistent ductus arteriosus Botalli, atrial septal defect, ventricular septal defect, and atrioventricular septal defect, which are more common in women, and aortic valve stenosis, bicuspid aortic valves, coarctation of the aorta, and transposition of the great arteries, which are more common in men [12,15]. No clear explanation exists for these sex-associated imbalances. In light of this, the effect of sex on the prognosis itself cannot be disregarded [12]. Although CHD is thought to be genetically determined, so far, only a few genes linked to the occurrence of heart defects have been identified. Therefore, in addition to genetic factors, environmental influences are likely to be partly responsible for CHD [11]. On the other hand, differences could also reflect the extent to which CHD prevalence at birth is known [17]. Perhaps, similar to other defects [18], racial/ethnic differences in the study populations may affect reported prevalence and sex distribution.

4.2. Cardiac and non-cardiac comorbidities

Gender differences in comorbidities and prognosis have not yet been sufficiently explored in CHD, but may be of particular relevance over the long term [12]. Some previous data have indicated an increased risk of developing pulmonary hypertension in female ACHD [12,19]. On the other hand, women have a reported 33% lower risk of complications of aortic diseases (aneurysms, dissections, and operations), a 47% lower risk of endocarditis, a 12% lower risk of relevant arrhythmias, and a 55% lower need for implantation of a cardioverter defibrillator (ICD) [12]. In the current study, the overall prevalence of comorbidities was higher in female than in male ACHD (62.5% vs. 46.6%). Arrhythmias, pulmonary hypertension, and neurological impairment were reported significantly more often by female participants, whereas coronary artery disease was reported significantly more often by male participants. The female predisposition to pulmonary hypertension and its relation to estrogen is well known [11]. With an odds ratio (OR) of 1.79 ($p = .001$), the female ACHD in the current survey seemed to have a much higher risk for the development of pulmonary arterial hypertension than suggested in registry data (OR = 1.33) [12,19,20]. Our findings regarding cardiac arrhythmias were likewise inconsistent with the current literature, which reports symptoms of cardiac arrhythmias to be more common in female than male ACHD [8,12]. Whether female sex is a protective factor against arrhythmia needs further consideration in future clinical research. The women in our survey reported a significantly higher prevalence of neurological restrictions (OR: 1.42; $p = .031$). This observation is reinforced by the fact that the incidence of neurological events usually increases in women with advancing age, often resulting in more serious consequences than in men [21]. In the current study, male ACHD reported coronary artery disease significantly more often than female ACHD. This can be partly explained by the fact that women tend to develop coronary artery disease up to ten years later than men [22]. As our study population's mean age was 41.9 ± 17.1 years and there were no significant differences between the sexes, long-term studies on coronary artery disease in ACHD are also warranted. Although the psychological needs of ACHD have recently received increasing attention [23,24], to date there have been no gender-specific studies on mental stress in ACHD. Whether psychological problems actually occur more frequently in women or whether gender-related social/role expectations distort the results is a question to be determined in future psychological/clinical investigations.

4.3. Healthcare of ACHD

Our study showed that for more than 90% of all male and female ACHD, PCPs, including general practitioners and specialists in internal and general medicine, are the first contact for medical problems. For specific CHD-related problems, more than 50% of ACHD first consulted their PCP. However, significantly more men than women primarily consulted their PCP and not a cardiologist (57.4% of male vs. 50.3% of female participants; $p = .001$). This observation corresponds with recent findings by Thore et al. that German men tend to prefer to visit a PCP, while women prefer specialists [25]. An important and alarming observation was that a remarkable 44.7% of female and 47.2% of male ACHD were unaware of existing ACHD-specialized institutions, such as ACHD-certified adult and pediatric cardiologists, regional ACHD facilities, and tertiary ACHD care centers. A recent study on the healthcare of ACHD in Germany (http://www.vemah.info) was able to show that these information deficits exist not only among patients, but also among their PCPs [26,27]. As the present study also supports this observation, it is essential to increase awareness of ACHD-specialized institutions, both for patients and their referring physicians. The same can be applied to "patient organizations for ACHD", as only 33.2% of female and 28.0% of male ACHD were informed of the existence of such organizations. This level of deficiency in knowledge about medical care structures and patient organizations among female ACHD is astonishing, since according to a recent study, women more often search for help or medical advice, because they perceive symptoms more often/earlier than men and are more likely to consider themselves in need of treatment [28]. In contrast with previous studies that detected no gender differences, in the present study, women rated the healthcare for their CHD in Germany as significantly worse than men did [29,30]. Regarding healthcare in ACHD some criticism must be directed towards the study center. Although the German Heart Center Munich is the largest center in Germany for the care of ACHD, many of the patients treated are obviously unaware of this fact. Most patients of the Heart Center are in a continuous follow-up for years or decades.For them this is routine. Since they do not perceive deficits in cardiological care, they are not thinking about care structures. This lack of awareness is most likely due to inadequate educational and information work by the Heart Center and needs urgent improvement.

4.4. Counselling needs

For many years, CHD in adults was the most understudied field of modern cardiology. This has improved, but even today there remains a lack of information on medical and cardiological aspects of CHD in adults, as well as unmet needs for general advice by ACHD [31]. As the current study data shows, this applies to areas of daily life, such as health insurance, life insurance, physical capacity, employability, and pregnancy. The present study indicates that both genders have a high need for counselling. Women in particular felt that their need for disease-specific information was insufficiently covered and stated a considerable need for information, especially regarding exercise capacity, resilience in everyday life, pension, pregnancy, rehabilitation measures, severe disability, genetic counselling, driver's license, and respiratory capacity to fly. This is in line with psycho-cardiological findings that indicate that gender role appears to be an important determinant of the perception of a person's cardiological disease, and that this affects their behavior. The male gender role implies rational, achievement-oriented and demanding behavior with help-seeking behavior indicating weakness. The female gender role implies stronger social integration, and as a result, a greater acceptability of help-seeking behavior [32]. Therefore, gender role typically affects how patients cope with a cardiological disease [33] and thereby affects their counselling needs. The Canadian MHART study [34] even showed that, as a consequence of gender differences, different forms of psycho-social treatment are advisable. Since the level of knowledge of patients is generally considered to be an important factor in achieving adequate health-related behavior [35], it is crucial that any gaps in knowledge be filled through structured, multidisciplinary counselling by specialists.

4.5. Quality of life

In terms of QoL, female ACHD reported greater impairments than their male counterparts, especially in the dimensions of activities of daily life, pain/physical complaints, and anxiety/depression. This resulted in an overall lower perceived QoL in women. Most studies, independent of the study population included, conclude that, compared with men, women are more likely to report an overall poorer QoL [36]. This also appears to be the case for ACHD. In an Asian study of QoL in ACHD, female sex was associated with poorer physical and psychosocial functioning [37]. Although the underlying mechanism remains unclear, it seems plausible that findings may be linked to gender-related psychosocial factors, such as personality traits, distress, and family support, rather than biological sex per se. Even though the EQ-5D-5L is only a generic instrument, our results suggest that further research, especially regarding self-care, pain/discomfort, and anxiety/depression, may enhance our understanding of how to improve QoL in ACHD, especially in women with CHD.

4.6. Limitations

The present results should be interpreted in light of certain limitations. First, only patients who voluntarily agreed to participate were enrolled. The nature of the patients' motivation to participate remains unknown and may have been biased by the Hawthorne effect. Secondly, only PROMs were surveyed in this study. As a result, the medical data reported by the participants have not been validated by an ACHD specialist and therefore do not necessarily match the data from the actual medical reports. Third, this study was performed at a national tertiary ACHD center. Thus, the sample of patients may not represent typical ACHD populations seen by PCPs or by non-specialized cardiologists. The prevalence of more complex anomalies is likely to be higher in a tertiary ACHD center than in either community-based hospitals or in cardiology departments. Another limitation is that sex and gender were not able to be separately assessed within the present study design. Failing to account for the difference between sex and gender during data collection may have led to spurious results. However, the data are largely in line with the literature on gender effects in medicine [32]. Lastly, the presented data derived solely from patients living in Germany. Generalization of the conclusions to patients living in other countries or different ethnic groups may or may not be valid.

5. Conclusion

Despite physiological differences between male and female patients, clinical training and research in ACHD has long been considered gender-neutral or focused on the male gender. Today, modern medicine increasingly observes gender differences that indicate the need for adjustment of treatment decisions and patient management [32,34]. Previous research on gender-based differences has not considered ACHD. The present research demonstrates that gender-based differences need to be taken into account in ACHD. Our study should be considered as merely a starting point. Major research gaps regarding gender differences in ACHD are waiting to be filled.

Based on our results, there is an urgent need for gender-sensitive, specialized, and integrative medical care for ACHD. In addition, PCPs must be sensitised about the importance of gender differences in ACHD, since they are the first point of contact for medical problems for the majority of ACHD, especially for men. Therefore, relevant guidelines should be established to take into account gender-related differences in diagnosis, pathogenesis, pharmacokinetics/dynamics, therapy, prognosis, long-term course, and prevention. In order to further improve medical care for patients, the long-term goal should be to take these differences into account in the education and training of future generations of physicians. All ACHD patients, but especially female patients, had an increased need for counselling. Moreover, ACHD - regardless of gender - are largely uninformed about the specialized care structures available to them, and therefore may not be receiving adequate care as required by their condition. It must be the goal of all health care providers involved in the care of ACHD to fill these gaps. Specific and holistic counselling could have a positive effect on the level of knowledge of the affected patient population, leading to improved quality of life, as well as reduced morbidity and mortality in the long term. Since many biological and psychosocial differences between male and female ACHDs have not yet been clarified, further research is needed.

Contributions

(I) Conception and design: SF, RN, HK; (II) Administrative support: All authors (III); Provision of study materials or patients: SF, RN, HK (IV); Collection and assembly of data: SF, LP, RN; (V) Data analysis and interpretation: SF; (VI) Initial manuscript writing: SF; (VII) Final approval of manuscript: All authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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4.2 Scientific Publication 2 *(published in „ Cardiovascular Diagnosis and Therapy “, IF 2.845)*

Provision of Medical Health Care for Adults with Congenital Disease associated with Aortic Involvement

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Original Article on Current Management Aspects in Adult Congenital Heart Disease (ACHD): Part III

Provision of medical health care for adults with congenital heart disease associated with aortic involvement

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Background: All patients with congenital heart disease (CHD) are chronically ill from their cardiac disease. Despite the increasing evidence that aortic alterations are becoming relevant, the importance of aortopathy in CHD has long been underestimated. This study was conducted to determine the health status of patients and/or the provision of health services of adults with CHD (ACHD) with manifest aortopathy or at risk thereof.

Methods: In a questionnaire-based cross-sectional survey, the "real life"-care of ACHD was analysed, comparing patients with risk of developing aortopathy and/or manifest aortopathy.

Results: Of the 563 enrolled ACHD (49.6% female, mean age 35.8±12.1, 18–86 years) 56.8% (n=320) had a risk of developing aortopathy and/or manifest aortopathy. Of the 320 patients at risk, 187 (33.2% of the total number) had a proven aortopathy. Within this subgroup, the basic medical care for CHD-independent medical problems was given by primary medical care providers [family doctors/general practitioners (GP) in 89.4% (n=286), internists in 13.4% (n=43), physicians of another specialty in 2.5% (n=8)]. Almost all primary medical care providers knew about the CHD of their patients. Even for CHD-specific health problems, the basic medical care of risk patients was provided by a family doctor or GP in 56.6% (n=181) and by an internist in 18.4% (n=59). 30.0% (n=96) primarily consulted another specialist, including cardiologists. Only 32.8% of ACHD at risk had ever been referred to a CHD specialist by a GP for cardiac problems related to their CHD. In contrast, the need for advice was high for ACHD with aortopathy and related mainly to physical activity, employment and education, pregnancy, rehabilitation or health and life insurance. Only 35.5% of patients at risk indicated that their information on specific care structures for ACHD was sufficient, and a further 38.1% of patients were aware of patient organizations.

Conclusions: Even today, aortic involvement in ACHD is an often-overlooked condition, although considerable negative effects on morbidity and mortality exist. As aortopathy gains in importance with increasing age and complexity of CHD, almost all affected ACHD need lifelong medical advice and access to modern, scientifically based care concepts. According to the study-results, primary care providers and also patients are mostly insufficiently informed about the specialized ACHD facilities. The future goal is therefore to create a better awareness of CHD problems among both primary care physicians and the patients concerned.

Keywords: Congenital heart disease (CHD); adults with congenital heart disease (ACHD); aortopathy; follow-up; care; prevention

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Introduction

Congenital heart anomalies are the most common isolated congenital organ malformations with an estimated incidence of 8/1,000 live births for congenital heart disease (CHD) and every year more than 1.35 million children are born worldwide with CHD (1-3).

Today, almost all types of CHD have become amenable to surgical or interventional treatment and more than 90% of all affected patients reach adulthood (4-6). Accordingly, around 50 million adults with CHD (ACHD) live at present worldwide (1).

However, despite of all advances, ACHD are and remain chronically ill from their cardiac disease, and many affected patients still have residua and sequelae of their CHD which contribute to an increased morbidity and mortality compared to the normal population (7-13).

For most CHD, heart defect specific cardiac residua or sequelae have to be expected, including heart failure, cardiac arrhythmias, pulmonary vascular disease with pulmonary/pulmonary arterial hypertension and a risk of infective endocarditis (4,7,14).

In the meantime, there is increasing evidence that also aortic alterations become relevant in ACHD. However, the importance of aortic diseases in CHD has long been underestimated and remains an often-overlooked condition, although it gains importance with increasing age and complexity of CHD.

Because of the listed potential residua and sequels, almost all patients with native, interventional or surgically treated CHD require lifelong follow-up care. This is mostly offered by general practitioners, family physicians and general internists (i.e., "primary care"), sometimes by cardiologists and only in a minority of cases by specifically trained and experienced congenital cardiologists or by cardiac centers for ACHD.

The aim of the current survey was to acquire real world data on the health status of patients and/or the provision of health services in ACHD associated with aortic abnormalities by general practitioners, family doctors and general practitioners (i.e., "primary care providers").

We present the following article/case in accordance with the SURG guideline checklist (available at http://dx.doi.org/10.21037/cdt-20-359).

Methods

Study cohort

In this cross-sectional clinical study, 563 patients from a tertiary care center for ACHD (Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, Technical University Munich, Munich, Germany) were included. Patients were consecutively included in the order that they presented at the institution and were not selected in prior. The study was part of a nationwide study to assess the care situation of the ACHD throughout Germany ("VEmaH study"). The survey has been approved by the institutional review boards of the Technical University Munich (157/16 S) and written informed consent was obtained from all participating patients before the start of documentation. Participation or non-participation in this study had no influence on the medical care of the patients. Guidelines on good pharmacoepidemiological practice (GPP) and data protection guidelines were followed.

Patient inclusion

Inclusion criteria for the present study were a confirmed diagnosis of CHD, and adult age (>18 years). Exclusion criteria were lack of cognitive competence to consent to research, and refusal to consent.

Medical records were reviewed for patient demographics, cardiac and non-cardiac diagnosis. Accordingly, patients were assigned to one out of six classes of diagnosis.

Questionnaire

As this is the first study to explore the "real world data" on the health status of patients and/or the provision of health services in ACHD, it was not possible to use a

standardized and validated questionnaire. For this purpose, a questionnaire was specifically devised in cooperation with the Chair of Behavioral Epidemiology at the Technical University of Dresden and the German Heart Center Munich as tertiary care center for ACHD.

This questionnaire contains questions related to the sociodemographic situation, the CHD, co-morbidities, care providers for medical problems in general and CHD-related problems, individual demands of the patients for counselling, knowledge of specific care structures and problems with the care situation from the patient's perspective. The questionnaire was completed either directly during the stay at the hospital or online on the homepage of the study (http://www.vemah.info).

Patient classification

At first stage, the patients were classified according to the underlying CHD and consecutively assigned to 1 of 6 major diagnosis groups depending on the type of the underlying CHD: complex CHD (I), disorders of the left heart/ anomalies of the aortic valve or aorta (II), disorders of the right heart/ anomalies of pulmonary valve or pulmonary artery (III), primary left-to-right shunt lesions—either at pre-tricuspid or post-tricuspid level (IV), genetic syndromes (V), or other congenital non-classifiable congenital heart anomalies (VI).

According to the underlying pathological anatomy, pathophysiology, and epidemiological data from the recent literature, ACHD were divided into the two groups "at risk for developing aortopathy and/or manifest aortopathy" or "without risk of intrinsic aortopathy".

The "aortopathy" in the current cohort was defined either depending on the underlying disease with "intrinsic" pathologic aortic alterations or depending on the reported absolute diameter of the aortic root or the ascending aorta. "Intrinsic" pathologic aortic alterations with abnormality of vessel architecture were presumed according to data from the literature for syndromic and non-syndromic congenital or hereditary congenital anomalies (15).

In the present survey, an absolute diameter of the aortic root or the ascending aorta of >38 mm in a normal sized adult was considered pathologic, without correcting the normal range for age, weight, sex or body surface area. This seems suitable for this overview survey, since the definition of a "normal aorta size" is still under discussion and robust data on aortic size in the "normal" population are missing (16), particularly in patients with CHD.

Statistical analysis

The data analysis was performed using SPSS 23.0 (IBM Inc., Armonk, NY, USA). All statistical evaluations of the data were pseudonymized and not person-related.

Descriptive statistical methods were used for data analysis and initial characterization of the study population. Differences between the groups were checked and evaluated using Chi-squared tests. *T*-tests were used for comparisons between mean values. Continuous data was expressed as mean ± standard deviation, categorical or interval scaled variables as absolute numbers or percentages. All occurring P values and tests for significance were performed two-sided. A P value <0.05 was considered significant.

Since multiple answers were permitted for some questions, the number of received answers may differ from the total number of study participants included.

Results

Study sample and patient characteristics

A total of 563 patients with a proven hereditary or congenital heart defect were suitable for the present analysis and were enrolled. The underlying anomaly could be assigned to one of six different main groups (I–VI) (*Table 1*). Out of the 563 consecutively enrolled patients with CHD 320 (56.8%) had a risk of developing aortopathy. Of the 320 patients at risk, 187 (33.2% of the total number) had a proven aortopathy according to medical notes or by definition (*Table 1*).

Epidemiological data

The mean age of all patients at the time of the survey was 35.8±12.1 years (range, 18 to 86 years). Most patients were in their third, fourth and fifth decade of life (n=455; 80.8%). Thirty-five patients (6.2%) were younger than 20 years, 73 older than 50 years (13.0%). In terms of gender distribution, 279 patients (n=49.6%) were female.

Comparing the age distribution within the two groups "at risk/manifest aortopathy" and "without intrinsic aortopathy", the patients at risk were significantly younger [34.3±10.8 years (range, 18 to 86 years) versus 37.7±13.3 years (range, 18 to 77 years)] and female patients were fewer [40.3% (n=129 of 320) versus 61.7% (n=150 of 243)].

The body mass index of all included patients was 24.7±4.4 kg/m^2 (range, 13.8–49.3 kg/m^2), with no significant difference between both groups at risk/manifest aortopathy

Table 1 Main diagnosis of the included 563 patients with congenital heart disease with/without aortopathy and also the number of patients with proven aortopathy according to medical notes or by definition

Congenital heart disease	Total number (%) of patients	At risk for developing aortopathy	Proven aortopathy (according to medical notes or by definition**)
I. Complex anomalies	148 out of 563 (26.3%)	74 out of 148 (50.0%)	–
Discordant atrio-ventricular or ventricular arterial connections, including:	86	64	–
Transposition of the great arteries	61	61	6
TGA-atrial switch	43	43	2
TGA-arterial switch	15	15	3
TGA-Rastelli	3	3	1
Congenitally corrected TGA	22	–	–
Double outlet right ventricle-TGA	3	3	1
Univentricular hearts, including:	23	–	–
Double inlet ventricle	9	–	–
Tricuspid atresia	14	–	–
Pulmonary atresia with intact septum	6	–	–
Truncus arteriosus communis	4	4	4
Other complex CHD including:	29	6	2
Ebstein's anomaly	23	–	–
Others	6	6	–
II. Anomalies of the left heart, the aortic valve or aorta	124 out of 563 (22.0%)	124 out of 124 (100.0%)	–
Bicuspid aortic valve/aortic valve anomalies	52	52	38**
Aortic stenosis (sub- and supra-valvular)	9	9	2**
Interrupted aortic arch	2	2	2**
Aortic coarctation	61	61	61**
III. Disorders of the right heart/anomalies of pulmonary valve or pulmonary artery	98 out of 563 (17.4%)	75 out of 98 (76.5%)	–
Tetralogy of Fallot	54	54	14
Double outlet right ventricle of Fallot type	7	7	3
Pulmonary atresia with ventricular septal defect	14	14	10
Pulmonary valve anomaly and pulmonary artery anomaly	23	–	–
IV. Primary left-to-right shunt lesions at pre-tricuspid or post-tricuspid level	130 out of 563 (23.1%)	11 out of 130 (8.5%)	–
Atrial septal defect	38	1*	1*
Persistent foramen ovale	14	1*	1*
Partial atrio-ventricular septal defect	8	2*	2*

Table 1 (*continued*)

Table 1 (*continued*)

Congenital heart disease	Total number (%) of patients	At risk for developing aortopathy	Proven aortopathy (according to medical notes or by definition**)
Partial anomalous pulmonary venous return	2	–	–
Total anomalous pulmonary venous return	4	–	–
Ventricular septal defects	45	3*	3*
Complete atrio-ventricular septal defect	15	–	–
Patent ductus arteriosus Botalli	4	4	1**
V. Genetic syndromes	35 out of 563 (6.2%)	35 out of 35 (100.0%)	–
Marfan- or Loeys-Dietz syndrome	29	29	29**
Aortic aneurysm of unknown origin	6	6	6**
VI. Non-classifiable CHD ("other")	28 out of 563 (5.0%)	1 out of 28 (3.6%)	–
Congenital cardiomyopathy	5	–	–
Congenital valve anomaly	11	1	1
Congenital other	12	–	–
Total	563	320	187

*, without expected risk of aortopathy, but with manifest aortopathy according to the medical records; **, aortopathy by definition. CHD, congenital heart disease; TGA, transposition great arteries.

(24.6±4.1 kg/m^2; range, 13.8–41.9 kg/m^2) compared to the group w/o intrinsic risk (24.9±4.8 kg/m^2; range, 16.4–49.3 kg/m^2) (P=0.480).

Basic medical care for general, CHD-independent medical problems

As shown by the study data, basic medical care was in the entire group of ACHD in 88.9% (n=501 answers) provided by family doctors, general practitioners, internists and sometimes physicians of another specialty as first consultation partners.

When asked about their primary medical care provider for general, CHD-independent, medical issues, in the group "at risk/manifest aortopathy" 337 answers were given. Eighty-nine point four percent (n=286) of the responders consulted a general practitioner/family doctor in such cases, while 13.4% (n=43) contacted an internist. Only 2.5% (n=8) of the patients indicated that their first correspondent had a different medical specialization (multiple answers possible).

In the group "without intrinsic aortopathy" 264 answers were received. In 88.5% (n=215) of cases, a general practitioner/family doctor was primarily consulted, in 13.2% (n=32) an internist, in 7.0% (n=17) a physician with another medical specialization (multiple answers possible).

In the entire group, according to the study participants, 94.3% of the above-mentioned primary medical care providers were aware that the patient has a CHD. The remaining 5.7% of the providers were unaware of their patients' CHD or the study participants stated that they did not know whether their primary care provider had knowledge of their existing CHD. There was no significant difference between the groups "at risk/manifest aortopathy" or "without intrinsic aortopathy".

Basic medical care for CHD-dependent medical problems

In response to the question on the primary contact physician for CHD-specific health problems, 585 answers (multiple answers possible) were received. Even in the case of heart problems, in the group "at risk/manifest aortopathy", 56.6% (n=181) of the responders were cared for by a general practitioner/family doctor, 18.4% (n=59) by an internist, and 30.0% (n=96) patients primarily by a doctor with a different specialization, including cardiology.

Similarly, in the group "without intrinsic aortopathy" 51.0% (n=124) of the patients primarily consulted a general

Table 2 Counselling needs and requests of all patients with congenital heart disease, patients "at risk for aortopathy" and in patients "without risk of intrinsic aortopathy"

Counselling needs and requests	Overall, % [n]	At risk for aortopathy, % [n]	"Without intrinsic aortopathy", % [n]	P value
Exercise capacity	44.9 [253]	45.9 [147]	43.6 [106]	0.584
Everyday burden	38.0 [214]	39.1 [125]	36.6 [89]	0.555
Age insurance	32.9 [185]	34.4 [110]	30.9 [75]	0.039*
Life insurance	29.3 [165]	30.6 [98]	27.6 [67]	0.561
Health insurance	28.6 [161]	26.9 [86]	30.9 [75]	0.776
Pension, retirement	29.7 [167]	30.0 [96]	29.2 [71]	0.841
Career opportunities	28.2 [159]	28.1 [90]	28.4 [69]	0.944
Severe disability	28.8 [162]	30.6 [98]	26.3 [64]	0.266
Rehabilitation measures	24.3 [137]	25.3 [81]	23.0 [56]	0.535
Pregnancy	26.6 [150]	22.8 [73]	31.7 [77]	0.018*
Genetic counselling	20.6 [116]	20.6 [66]	20.6 [50]	0.989
Airworthiness	16.9 [95]	14.4 [46]	20.2 [49]	0.069
Education forms	6.4 [36]	5.6 [18]	7.4 [18]	0.392
Driving license	4.4 [25]	3.8 [12]	5.3 [13]	0.361
Other needs	2.7 [15]	0.6 [2]	5.3 [13]	0.001*

*, significant. n, absolute number.

practitioner/family doctor, 18.5% (n=45) an internist, and 32.9% (n=80) primarily a doctor with a different specialization, including cardiology.

Transfer to an institution specialized in CHD because of a medical problem

Only 32.8% (n=105) of CHD-patients "at risk/manifest aortopathy" reported that a general practitioner/family doctor had referred them to a CHD-specialist in the past because of cardiac problems related to their CHD. Forty-nine-point-four percent (n=158) have never been referred to a CHD-specialist.

Also, in the group "without intrinsic aortopathy", only 33.7% (n=82) of patients had been referred to a CHD-specialist because of cardiac problems related to their CHD. Even 49.4% (n=120) have never been referred to a CHD-specialist.

Specific counselling needs for advice for patients with CHD with and without aortopathy

The question in which areas a specific advice is required was answered by the study participants with multiple responses. In all groups, the greatest need for counselling was reported with respect to the ability to perform during physical or sporting activity, to employment and education, to pregnancy and inheritance, to rehabilitation measures, and also to driving license, the ability to travel and to air travel. Moreover, there was also a specific need for information about health insurance, life insurance and retirement (*Table 2*).

Patients knowledge about targeted care for ACHD in Germany

All patients were asked about the awareness of certificated facilities for the care of ACHD. Certificated and accredited pediatric cardiologists, adult cardiologists, specialized hospitals and heart centers for ACHD were widely unknown to the majority of all affected patients. There was no significant difference between both groups of "ACHD at risk" and "without risk of intrinsic aortopathy".

The question of whether the information on specific care structures for ACHD is sufficient was answered by 293 of the 320 participating ACHD "at risk" [91.6%; missing data

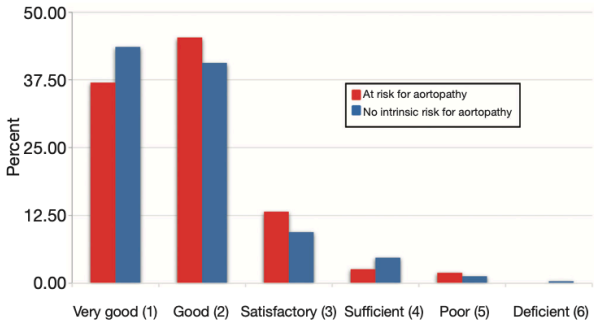

Figure 1 Patients' satisfaction in the context of medical care for their congenital heart defects in percent (%).

in 27 (8.4%)]. Only 35.5% (n=104 of 293) participating patients answered positively, another 29.4% (n=86 of 293) were undetermined. In patients "without risk of intrinsic aortopathy" 224 of the 243 participants answered [92.2%; missing data in 19 (7.8%)]. Only 33.0% (n=74 of 224) participating patients answered positively, another 29.5% (n=66 of 224) were undetermined. There was no significant difference between both groups (P=0.812).

Patients knowledge about patient organizations for ACHD in Germany

All patients were asked whether they knew patient organizations for ACHD. This question was answered by all 563 study participants. Similar to targeted medical institutions, patient organizations for ACHD were also widely unknown to the majority of affected patients.

In the group of ACHD "at risk" the question was answered positively by only 38% (n=122) of participating patients, another 10% (n=32) were undetermined. In patients "without risk of intrinsic aortopathy" also only 35% (n=86) participants answered positively, another 12% (n=30) were unsure (*Figure 1*). There was no significant difference between both groups (P=0.615).

Patient satisfaction in the context of medical care for their CHD

The question concerning satisfaction in the context of medical care for their CHD was answered by 545 study participants (missing data n=18). On a scale of 1–6 (1= very good; 6= unsatisfactory), 311 patients with aortopathy (missing data n=9) rated their medical care on average 1.87 (very good–good). The 234 patients (missing data n=9) without risk gave an average 1.81 (very good–good). There was no significant difference between both groups (P=0.414) (*Figure 1*).

Discussion

Clinical relevance of the study

This is the first study to explore the medical care provided by primary care physicians (family doctors, general practitioners, or internists) within a large sample of adults with almost all types and severities of CHD and associated risk of having or developing an aortopathy.

Our data indicate that, even in this vulnerable patient group, family doctors and/or general practitioners are in fact the first medical care providers when a general medical problem arises. These first physicians consulted include family doctors and/or general practitioners in 89.4%, internists in 13.4%, and physicians of another specialty in 2.5% (multiple answers permitted). It is remarkable, that almost all of these physicians are aware that their patient has a CHD.

It is however of concern that family doctors and/or general practitioners and internists are also the first consultants to be contacted for CHD-specific health problems. Under these conditions, family doctors or general practitioners are approached in 56.6%, internists in 18.4% and a doctor of another specialty, including cardiology, in at least 30% of cases. This is especially problematic, as many primary care physicians are usually not specifically trained, not experienced in CHD care and unaware of the long-term problems of ACHD. This may even have more severe consequences in view of the ever-growing number of CHD-patients, all of which are chronically ill due to residua and sequelae of the underlying cardiovascular abnormality. Therefore, the spectrum of long-term problems is so widespread that it can only be mastered by CHD-experienced specialists. As described initially, it includes in particular the residual and subsequent conditions specific to the heart defects, including heart failure, cardiac arrhythmias, pulmonary vascular disease/pulmonary hypertension and endocarditis.

In addition, depending on the underlying congenital heart anomaly, aortic alterations become more and more relevant with increasing age. Nevertheless, aortic involvement in CHD remains an often-overlooked condition, although considerable negative effects on morbidity and mortality exist (17).

Aortopathy in genetically determined, syndromic disorders with aortic involvement or in patients with CHD

Aortopathy, defined as progressive dilatation of the proximal aortic root, ascending or descending aorta, is frequently found in genetically determined, syndromic disorders with aortic involvement (e.g., Marfan-syndrome), as well as in the natural or in the postoperative / postinterventional course in CHD (18).

"Aortopathy" is generally characterized by degeneration of the aortic wall layer with aortic medial degeneration, which is associated with aortic dilation or aneurysm formation as well as aortic-ventricular interaction (15).

Aortic medial degeneration is well recognized and reaches its most severe form in genetic determined disorders like Marfan syndrome with annuloaortic ectasia. It is also seen in Loeys-Dietz syndrome, other connective tissue disorders with vascular involvement such as vascular Ehlers-Danlos syndrome, as well as Turner- or Noonan-syndrome (19).

The changes in aortic medial degeneration are inappropriately called "cystic medial necrosis", although no "cysts" can be found histopathologically. This process is rather characterized by elastic fiber degeneration and fragmentation, non-inflammatory loss of smooth muscle cells, and with accumulation of basophilic ground substances within cell-depleted areas in the media (20).

In other CHD, the above mentioned aortic medial degeneration is qualitatively similar, but seldom quantitatively so pronounced as in Marfan syndrome. Such alterations occur not only in complex but also in simple CHD. In conotruncal anomalies, like Tetralogy of Fallot, pulmonary atresia, truncus arteriosus, the process of dilatation already starts in the prenatal period and the dilatation is flow-related. Besides, aortopathy reflects a common developmental fault that weakens the aortic wall and causes aortic dilatation, decreases aortic elasticity and increases aortic stiffness (14,18,21,22). At least in some congenital heart anomalies, the hypothesis of aortic dilatation has shifted from so called "poststenotic dilatation" to "primary intrinsic" aortopathy.

According to the literature, aortic dilatation and aortic aneurysms occur or develop in many different CHD. Aortopathy is associated particularly with a bicuspid aortic valve, aortic coarctation, conotruncal anomalies such as tetralogy of Fallot, pulmonary atresia with ventricular septal defect, complete transposition of the great arteries, truncus arteriosus communis, double outlet right/left ventricle, or aorto-pulmonary window or aortic arch anomalies. Also, certain patients with univentricular hearts or hypoplastic left heart syndrome after modified Fontan-operation are susceptible (23-26). In addition, aortopathies are frequently seen after any operative treatment involving the aorta, e.g., after arterial switch operation for transposition of the great arteries, or after Ross-operation.

The assumption that the aorta is affected in many CHDs is supported by the large numbers of unselected patients in the present study, where out of the 563 consecutively enrolled ACHD, 320 (56.8%) had a risk of developing aortopathy and/or manifest aortopathy. A proven aortopathy had 57.9% (n=185) of the patients at risk (n=320) and 32.5% of all included patients (n=563). The patients at risk for developing aortopathy and/or manifest aortopathy were predominantly from the group of complex CHD [74 out of 148 (50.0%)], anomalies of the left heart, of the aortic valve or the aorta [124 out of 124 (100.0%)], disorders of the right heart/ anomalies of pulmonary valve or pulmonary artery [75 out of 98 (76.5%)] or, genetic syndromes with aortic involvement [35 out of 35 (100.0%)].

Clinical relevance of aortopathy in patients with CHD

Clinically relevant is the fact, that such an aortopathy may progress and put the affected patients at risk for aortic aneurysm formation and aortic dissection or rupture.

In order to prevent such devastating aortic complications, particularly aortic dissection or rupture, it would be essential to identify high-risk patients at an early stage and, if necessary, to treat them prophylactically or to provide them with appropriate surgical treatment in a timely manner.

Thereby, it is important to know that the decision-making process is strongly dependent on the underlying diagnosis of the CHD or the underlying disease (e.g., Marfan syndrome).

For the medical prophylaxis of the progression of aortic widening, for example, data are available for patients with Marfan syndrome at best, but not for aortopathies in other forms of CHD.

It should also be noted that the indication for prophylactic surgery in adults with acquired, degenerative forms of aortic aneurysm only apply to a limited extent to aortopathies in CHD.

Moreover, aortic dilatation and increased aortic stiffness can induce progredient aortic valve regurgitation, left ventricular hypertrophy, reduced coronary artery flow and left ventricular failure (21,22,27).

The care of patients with aortopathy in patients with CHD

All these facts indicate that ACHD require targeted care and follow-up by experienced specialists.

Starting around the year 2006, in Germany for this reason, pediatric cardiologists and cardiologists who had sufficient experience in the care of ACHD have been certificated. In addition, medical practices, specialist clinics and centers for the care of ACHD were also accredited.

In the meantime, similar to Canada, as of 03/2020 Germany has a nationwide network of more than 348 certified pediatric cardiologists and cardiologists in private practice, 11 certified regional centers and 19 certified supra-regional, tertiary care centers for ACHD. However, as reflected by preliminary data of the VEmaH-study, the problem is that most patients with CHD in Germany do not reach these centers at all (28-30). This fact is consistent with the patients' statements, that about 50% of the surveyed patients indicated that they have never been referred to a CHD specialist for cardiac problems related to their CHD. It could also be explained, at least in part, by the globally known "loss to follow" phenomenon.

In addition, also the knowledge of patients about the nationwide availability of specialists and centers for the treatment and follow-up of their CHD is completely inadequate. Only 36% of all patients who responded indicated that their information on specific care structures for CHD was sufficient.

Furthermore, only 37% of all responders were aware of the existence of patient organizations for CHD.

Finally, some criticism must be directed towards the study center. Although the German Heart Center Munich is the largest center in Germany for the care of ACHD, many of the patients treated here and many referring physicians are obviously unaware of this fact. Most patients of the Heart Center are in a continuous follow-up for years or decades. For them this is routine. Since they do not perceive deficits in cardiological care, they are not thinking about care structures. This equally applies to the referring physicians.

However, the patient satisfaction with medical follow-up care mainly concerns cardiological aspects. Present study results suggest, that there is an unmet need for further information and consulting. This concerns in particular aspects such as exercise, nutrition, life style, rehabilitation, prevention and socio-medical aspects such as old-age security. This lack of awareness is most likely due to inadequate educational and information work by the Heart Center and needs urgent improvement.

Limitations

The present study engaged a remarkably large sample size of recruited patients with almost all types and severities of CHD. However, current results should be interpreted in the light of certain limitations.

First, only patients who voluntarily agreed to participate were enrolled. The extent to which the patients' motivation to voluntarily participate remains unknown and may have biased the observations, as patients who voluntarily participate in research surveys differ from those who choose not to participate.

Further, it is possible that the number of patients with manifest aortopathy is even higher than indicated. This may be likely due to the fact that only those patients were classified as "manifest", in whom an aortopathy was intrinsic or pathological aortic diameters were described in the medical records. The difficulties in interpreting the measured values can be explained by the fact that the aorta can often not be adequately visualized by routine transthoracic echo examinations. In adults, only the first few centimeters of the ascending aorta can often be seen. However, more advanced examinations, such as cardio-MRI, CT or aortography, which allow the entire aorta to be examined, were not routinely performed.

In addition to the absolute size of the aorta, the progression of the aortic diameter over the time would be important for the risk assessment of the affected patients. We have not considered this aspect in our study, as it was a cross-sectional study from the outset and not a longitudinal study.

This study was performed at a tertiary care center for ACHD. Thus, the sample of patients does not represent the typical population of CHD seen by a general practitioner or by a cardiologist. The prevalence of more complex anomalies in these institutions is likely to be higher than either in community-based hospitals or even in departments for cardiology.

Lastly, the presented data derive solely from patients living in Germany. Generalization of the conclusions and transmission to patients living in other countries or different culture groups is debatable.

Conclusions

Although today most patients with CHD survive into adulthood, many of them have relevant residua and sequels, including aortopathy. Even today it is not rarely overlooked, that such aortopathy can cause significant morbidity and mortality, particularly with increasing age. This does not only apply to the rapidly increasing number of adults with complex CHD, but also to simple treated or untreated CHD, which were considered harmless until recently. Therefore, the awareness of patients as well as treating

physicians about aortopathies and associated potential risks must be increased to close actual gaps in patient care.

An experienced routine follow-up care by specialized and/or certified physicians or centers is imperative for all patients with CHD, and in particular for those with intrinsic aortopathy or at risk for aortopathy.

Finally, as the presented data derive from people living in Germany, further studies are needed to assess the situation of CHD-patient care in other countries. In a next step further data from other countries might be collected for comparison purposes in order to establish practical international guidelines for the management of the increasing number of ACHD.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The survey has been approved by the institutional review boards of the Technical University Munich (157/16 S) and written informed consent was obtained from all participating patients before the start of documentation.

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Lessons from the Short- and Mid-term Outcome of Medical Rehabilitation in Adults with Congenital Heart Disease

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(II) Administrative support: All authors
(III) Provision of study materials or patients: All authors
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(V) Data analysis and interpretation: All authors
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(VII) Final approval of manuscript: All authors

Original Article

Lessons from the short- and mid-term outcome of medical rehabilitation in adults with congenital heart disease

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Background: The number of adults with congenital heart disease (ACHD) is steadily increasing. Over their life-time, many of the affected patients require medical rehabilitation after interventional or surgical treatment of residua, sequels or complications of their congenital heart defect (CHD). However, up to now only scarce data exist about indication, performance and outcomes of cardiac rehabilitation in ACHD.

Methods: The course and outcome of rehabilitation after previous interventional or surgical treatment in ACHD was analyzed in a retrospective cohort study.

Results: Two hundred and five ACHD {54% female; mean age 34±12 [16–68] years} with mild (23.9%), moderate (35.1%) or severe CHD (41.0%), of whom 32% had complex CHD, 21% right-ventricular outflow tract obstructions, 20% pre-tricuspid shunts, 18% left heart or aortic anomalies, 9% post-tricuspid shunts and 2% other congenital cardiac anomalies were included into analysis. The main indications for rehabilitation were a preceding surgical (92%) or interventional (3%) treatment of the underlying CHD immediately before rehabilitation. During rehabilitation, no severe complications occurred. The number of patients in function class I/II increased from 189 to 200 and decreased in class III/IV from 16 to 5. Cardiac medication could be reduced or stopped after rehabilitation in 194 patients, with the exception of ACE-inhibitors. There was an improvement in cardiovascular risk factors. While before medical treatment 77% (n=157) patients were capable of working, the number increased to 82% [168] at the end of rehabilitation. Throughout a follow-up 9.3% (n=19) of patients needed further cardiac interventions.

Conclusions: The current study provided for the first time comprehensive data on the course of rehabilitation in a large cohort of ACHD after surgical or interventional treatment. The overall outcome of ACHD after rehabilitation was uneventful and favorable. Further research is required to assess the clinical long-term outcome, the impact of rehabilitation on the quality of life, disease coping and employment. The results of this study can serve as a benchmark for the development of specific rehabilitation programs in ACHD.

Keywords: Adults with congenital heart disease (ACHD); prevention; medical health supply; primary health care; supply characteristics in congenital heart defects

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Introduction

Congenital malformations of the heart or the great arteries are the most common anomalies in humans, encompassing a great variety of anomalies from simple to complex congenital heart defects (CHD). If left untreated, at least the more complex lesions are often fatal in the first years of life (1). While in the 1940s, most patients with hemodynamically relevant CHD died before reaching adulthood, today up to 95% reach adulthood due to the prodigious diagnostic and therapeutic advances in cardiology, heart surgery, intensive care medicine and pharmacological treatment (2-4).

Although almost all CHD are amenable to treatment, CHD can only be repaired, not cured. Many surgical or interventional procedures result in anatomical and functional residua and sequels that cause health problems later in life and require lifelong dedicated follow-up (5,6). Typical residua and sequels of the specific treatment that negatively influence morbidity and mortality in adulthood encompass heart failure, cardiac arrhythmias, pulmonary vascular disease, aortopathy, endocarditis as well as acquired comorbidities (7-10). Therefore, most adults with congenital heart defects (ACHD) require specific rehabilitation measures, particularly after operations, re-operations, interventional or electrophysiological treatment of serious complications or diseases and after surviving sudden cardiac death.

The ultimate goal of rehabilitation measures in cardiology is to reduce cardiac morbidity and mortality (11,12). It is well known from the study of patients with acquired heart disease that after operations or serious illnesses, targeted cardiological rehabilitation can contribute to regain and maintain the best possible individual physical and mental health as well as social integration in the long term by reducing typical cardiovascular risk factors such as obesity, arterial hypertension, lipid disorders by improving physical performance, providing targeted psycho-cardiological care and social, occupational reintegration (13).

While rehabilitation programs for patients with acquired heart disease have been extensively studied, there are no comprehensive, evidence-based data on rehabilitation programs for ACHD (14). Therefore, the aim of the current study was to obtain first comprehensive data on the specific needs of ACHD requiring medical rehabilitation. Another objective was to develop a concept for the implementation of rehabilitation measures for ACHD on the basis of the acquired experience. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/cdt-20-727).

Methods

This is a retrospective cohort study on the medical care and rehabilitation of ACHD, initiated by the department of Congenital Heart Disease and Paediatric Cardiology of the German Heart Centre Munich in cooperation with the rehabilitation clinic “Klinik Höhenried”.

Inclusion criteria were the presence of a CHD, a completed rehabilitation measure, a medical follow-up and the written consent to participate in the study. Exclusion criteria were the lack of cognitive competence to consent to research and the refusal to consent.

The medical records of the inpatient stay and the follow-up were analyzed. Based on the patient’s medical history and the clinical assessment of the treating physicians, all patients were classified into one of four functional classes (according to PERLOFF) (5). This classification was developed specifically for ACHD and is similar to the NYHA classification of heart failure. Since the symptoms of functional classes I and II as well as III and IV are fluent, they were each grouped into a joint functional class I/II or III/IV for statistical analysis. Furthermore, according to the underlying heart defect, patients were assigned to one of three disease severity classes (simple, moderate, severe) following the recommendations of the American College of Cardiology (15).

The study protocol was reviewed and approved by the ethics committees of the participating institutions (project number: 5338/12). All included patients were informed in detail about the planned study in an explanatory interview and by written information. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients gave their written consent to participate in the study.

Participation or non-participation in this study had no

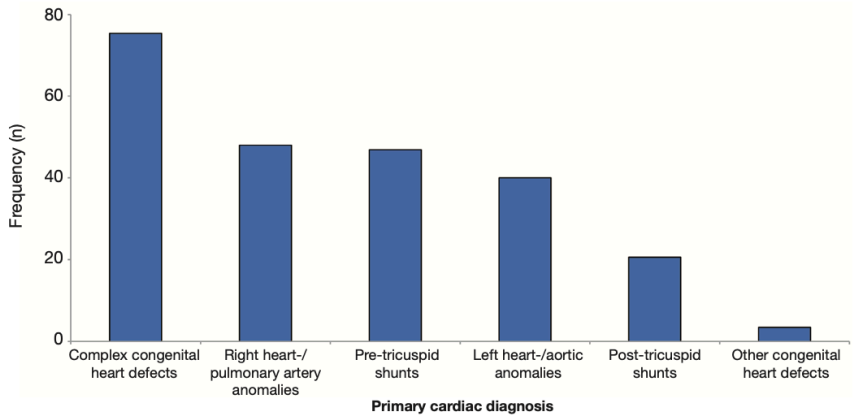

Figure 1 Frequencies of the main cardiac diagnoses: complex congenital heart defects, right heart-/pulmonary artery anomalies, pre-tricuspid shunts, left heart-/aortic anomalies, post-tricuspid shunts and other congenital heart defects.

influence on the medical care of the patients.

Data collection and processing were carried out in compliance with the respective federal and state data protection laws. All statistical analyses were made anonymously and not related to individuals.

Statistical analysis

Continuous data were expressed as mean ± standard deviation, median and range. Categorical or interval scaled variables were expressed as absolute numbers or percentages. The data analysis was performed using SPSS 25.0 (IBM Inc., Armonk, NY, USA).

Results

Study sample and patient characteristics

A total of 205 consecutively recruited ACHD, aged ≥18 years, were included in the present study. Two patients, who had not yet reached the numerical age of 18 years, were also classified as "adults" according to their maturity. A total of 110 patients (53.7%) were female. Median patient's age at the end of their hospital stay at the German Heart Center Munich was 31 years (range: 16–68 years; mean: 33.8±12.3 years).

Main diagnosis and assignment to "ACC Severity Code" Class

The main cardiac diagnoses were grouped into six categories: (I) complex anomalies, (II) anomalies of the right heart, pulmonary valve or pulmonary artery, (III) anomalies of the left heart, aortic valve or aorta, (IV) pre-tricuspid shunts, (V) post-tricuspid shunts, and; (VI) other anomalies.

Of the 205 included ACHD, 66 (32.2%) had complex heart defects, 42 (20.5%) had right heart/pulmonary abnormalities, 35 (17.1%) had left heart/aortic abnormalities, 41 (20%) had pre-tricuspid shunts, 18 (8.8%) had post-tricuspid shunts and 3 (1.4%) other congenital anomalies (*Figure 1*).

Ten patients had a syndromic disease associated with their cardiac abnormality: Trisomy-21 (Down syndrome) (n=4), Marfan syndrome (n=3), Microdeletion 22q11 (n=2) and Turner syndrome (n=1).

According to the recommendations of the American College of Cardiology, 49 patients (23.9%) could be assigned to the simple, 72 patients (35.1%) to the moderate and 84 patients (41.0%) to the complex CHD-group (*Figure 2*).

Previous surgical and/or interventional cardiac procedures

The number of procedures performed for each underlying heart defect is given in *Table 1*. Of all patients, 202 patients (98.5%) had at least one heart operation since birth due to their CHD (*Table 2*).

Of the patients operated, 110 (54.7%) were re-operated at least once because of their CHD, while an interventional treatment was performed in 41 patients (20.0%).

Several patients had up to six re-operations and up to

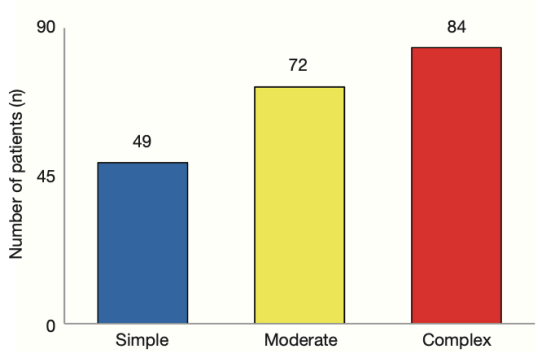

Figure 2 Classification of the 205 patients into a severity level (simple, moderate, complex) depending on the type of congenital heart defect, according to the recommendations of the American College of Cardiology (11).

two re-interventions (*Figure 3*).

Interventions performed at the German Heart Center Munich as an indication for rehabilitation measures

Immediately prior to the start of rehabilitation, 189 (92.2%) patients had reparative heart surgery, one patient (0.5%) palliative surgery and six patients (2.9%) an interventional treatment (*Table 3*).

In nine patients (4.4%), rehabilitation was not preceded by any surgical or interventional intervention. Of these nine patients, four [double inlet ventricle (n=2); DORV-Fallot type (n=1); tricuspid atresia (n=1)] had relevant arrhythmias requiring cardioversion or electrophysiological treatment.

An electrophysiological treatment for cardiac-arrhythmia was performed in 30 patients before rehabilitation, including pacemaker- (n=29) or ICD-implantation (n=1). Of these, 14 patients had atrial arrhythmias, one had ventricular arrhythmias, two had a second-degree and 13 had a third-degree AV block (*Table 4*).

Clinical data prior to the transfer from the German Heart Center to the Rehabilitation Clinic and Course of Rehabilitation

At the time of referral to the rehabilitation clinic, immediately after the end of hospital treatment, all patients were fully compensated and without signs of heart failure. Out of 205 patients, 189 (92.2%) were in PERLOFF Functional class I/II and 16 (7.8%) in Functional class III/IV, although 156 (n=76.1%) were classified as moderate or complex CHD, according to the ACC severity code, and 15 (7.3%) suffered from Eisenmenger syndrome or chronic cyanosis.

During the entire rehabilitation, no critical cardiac events occurred. None of the 30 patients with relevant arrhythmias, with a history of thromboembolic events (n=12) or infectious endocarditis (n=5) had a relapse during the rehabilitation period.

After a mean rehabilitation duration of 24 days (median: 21 days; range: 9–50 days) the number of patients in Functional class I/II increased from 189 to 200, with only five patients (Ebstein's anomaly; pulmonary atresia with ventricular septal defect; pulmonary valve stenosis; tricuspid atresia; double inlet ventricle) remaining in Functional class III/IV (*Table 5*).

At the time of transfer to the rehabilitation clinic, 95% of the patients were on chronic medication. After rehabilitation, the number of patients receiving diuretics, beta-blockers, amiodarone, digitalis glycosides, AT-blockers, Ca-Antagonists or oral anticoagulants decreased, while during the rehabilitation the prescription of all drugs increased (*Table 6*).

While prior to the medical treatment 157 patients were capable of working, the number increased to 168 after rehabilitation. Only 6 patients (2.9%) [Ebstein's anomaly (n=3), Ductus arteriosus (n=1), tetralogy of Fallot (n=1) and aortic valve regurgitation (n=1)] were discharged as "unable to work". This is equivalent to the 4% of patients who were actively working/job-seeking before the cardiac intervention.

Mid-term outcome after completion of the rehabilitation

Between discharge from rehabilitation and follow-up at the German Heart Center Munich (mean time interval 28 months, median: 22 months; range: 0–172 months), the number of patients in Functional class I/II decreased from 200 to 194, while the number in Functional class III/IV increased from 5 to 11 patients, including patients with atrial septal defect (n=1), tetralogy of Fallot (n=1), tricuspid atresia (n=1), Ebstein's anomaly (n=3), pulmonary atresia with ventricular septal defect (n=1), double inlet ventricle (n=1) and Ductus arteriosus (n=1). Cardiac decompensation occurred in four patients (2%) with Ebstein's anomaly, tetralogy of Fallot, complete transposition or atrial septal defect.

Treatment-relevant atrial arrhythmias (n=5) or a third-

Table 1 Congenital heart defects of the included patients: frequencies, previous procedures, age

Congenital heart defect	Frequency	%	Operation without/with	Intervention without/with	Age, median (range)
Atrial septal defect	39	19.0	0/39	29/10	31 [18–68]
Tetralogy of Fallot	32	15.6	0/32	26/6	31 [17–65]
Ebstein's anomaly	31	15.1	1/30	24/7	40 [19–64]
Aortic valve stenosis	14	6.8	0/14	11/3	29 [16–46)]
Transposition of the great arteries (TGA)	13	6.3	0/13	6/6	31 [19–45]
Coarctation of the aorta	13	6.3	0/13	12/2	31 [21–61]
Ventricular septal defect	11	5.4	0/11	8/3	26 [18–68]
Aortic valve insufficiency, congenital	8	3.9	0/8	8/0	36 [20–51]
Tricuspid atresia	8	3.9	1/7	4/4	34 [29–51]
Complete atrioventricular septum defect	6	2.9	0/6	4/2	25 [20–53]
Pulmonary atresia with ventricular septal defect	6	2.9	0/6	3/3	26 [21–40]
Double inlet ventricle	5	2.4	0/5	3/2	34 [23–43]
Congenitally corrected transposition of the great arteries	3	1.5	0/3	2/1	[18–52]
Double outlet right ventricle (Fallot type)	2	1.0	0/2	2/0	27–22
Double outlet right ventricle (TGA type)	2	1.0	0/2	1/1	24–27
Persistent foramen ovale	2	1.0	0/2	1/1	39–53
Pulmonary atresia	2	1.0	0/2	1/1	21–21
Pulmonary valve stenosis	2	1.0	0/2	1/1	29–65
Truncus arteriosus communis	2	1.0	0/2	2/0	26–44
Aortic aneurysm	1	0.5	0/1	1/0	19
Ductus arteriosus	1	0.5	1/0	1/0	27
Mitral valve insufficiency, congenital	1	0.5	0/1	1/0	24
Mitral valve prolapse, congenital	1	0.5	0/1	1/0	30
Total	205	100	3/202	152/53	31 [16–68]

Table 2 Treatment status of the 205 patients included

Treatment status	Frequency	In %
No procedure	3 out of 205	1.5
Surgical treatment and/or intervention	202 out of 205	98.5
• Surgical treatment (≥1)	202 out of 205	98.5
o Re-operation (≥1)	110 out of 201	54.7
• Interventional treatment (≥1)	41 out of 205	20.0
o Re-intervention (≥1)	11 out of 41	26.8

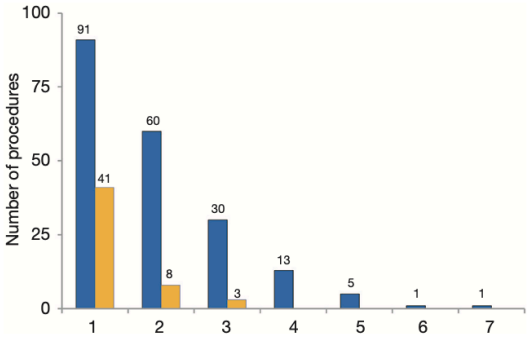

Figure 3 Number of operations, interventions and re-interventions for the 205 patients included.

degree AV block (n=1) occurred in patients with atrial septal defect (n=1), aortic valve stenosis (n=1), complete transposition (n=1), tricuspid atresia (n=1), or tetralogy of Fallot (n=2).

Between discharge from rehabilitation and the follow-up visit no patient was diagnosed with an infectious endocarditis. One 26-year-old woman with tricuspid atresia developed a thromboembolic event.

All in all, during follow-up, 19 patients (9.3%) needed further cardiac interventions (*Table* 7). One patient with persistent Ductus arteriosus was listed for lung transplantation and another patient (Ebstein's anomaly) refused recommended corrective surgery.

Table 3 Treatment at the German Heart Center of Munich, representing the indication for rehabilitation measures

Surgical treatment	Pre-rehabilitation measures, frequency (n)
ASD patch closure	42
Homograft implantation	32
Valvuloplasty	24
Mechanical valve replacement	19
Biological valve replacement	17
Conduit/vascular prosthesis	16
Valvuloplasty - and/or replacement + vessel (Bentall-/ David-OP)	14
VSD patch closure	8
Fontan operation	4
Pacemaker implantation	4
PFO closure	2
AVSD patch closure + cleft stitching	2
Mechanical valve replacement + Homograft	1
Mechanical valve replacement + VSD patch closure	1
Other interventions*	10
Total	196

*, resection of the atrial septum and a membrane at the inferior vena cava (partial anomalous pulmonary vein return), baffle revision and resection of an LVOTO (double outlet right ventricle, aortic coarctation, hypoplasia of the transverse aortic arch and PDA). Mustard-Brom-operation (TGA), coil-occlusion of the internal thoracic artery (pulmonary atresia with ventricular septal defect). Corrective surgery (sinus-venosus defect). Atrioseptostomy and aortopulmonary shunt (double inlet left ventricle), relocation of a left superior vena cava (TGA), total cavopulmonary anastomosis (congenitally corrected transposition), correction of a partial anomalous pulmonary vein return) (sinus-venosus defect), patch closure of aortal wall defects (ASD). ASD, atrial septal defect; VSD, ventricular septal defect; PFO, patent foramen ovale; AVSD, atrioventricular septal defect; LVOTO, left ventricular outflow tract obstruction; PDA, patent ductus arteriosus; TGA, transposition of the great arteries.

Table 4 Type of congenital heart defect in which a pacemaker or ICD implantation was performed immediately prior to rehabilitative measures

Cardiac diagnosis	Type of arrhytmia	Pacemaker	ICD
Aortic valve stenosis	AVB-3 (n=1)	1	0
Atrial septal defect	AVB-3 (n=1)	1	0
Coarctation of the aorta	AVB-2 (n=1); AVB-3 (n=1)	2	0
Complete atrioventricular septal defect	AVB-3 (n=1); SVA (n=1)	2	0
Congenitally corrected transposition of the great arteries	AVB-3 (n=1)	1	0
DORV-TGA	AVB-3 (n=1)	1	0
Double inlet ventricle	SVA (n=1); VA (n=1)	1	1
Ebstein's anomaly	AVB-3 (n=3); SVA (n=2)	5	0
Persistent Foramen Ovale	SVA (n=1)	1	0
Pulmonary atresia + VSD	SVA (n=1)	1	0
Tetralogy of Fallot	SVA (n=2)	2	0
Transposition of the great arteries	AVB-3 (n=3); SVA (n=2)	5	0
Tricuspid atresia	SVA (n=4)	4	0
Ventricular septal defect	AVB-2 (n=1); AVB-3 (n=1)	2	0
Total		29	1

AVB, AV-Block 2nd or 3rd degree; SVA, supraventricular arrhythmias; VA, ventricular arrhythmias; DORV-TGA, double outlet right ventricle - transposition of the great arteries type; VSD, ventricular septal defect.

Table 5 Type of congenital heart defect and number of patients in the various function classes according to Perloff at the time of rehabilitative measures at admission and discharge

Cardiac diagnosis	Before	After
	I/II versus III/IV	I/II versus III/IV
Atrial septal defect	38 // 1	39 // 0
Tetralogy of Fallot	31 // 1	32 // 0
Ebstein's anomaly	27 // 4	30 // 1
Coarctation of the aorta	12 // 1	13 // 0
Transposition of the great arterias	12 // 1	13 // 0
Tricuspid atresia	5 // 3	7 // 1
Pulmonary atresia with ventricular septal defect	5 // 1	5 // 1
Double inlet ventricle	4 // 1	4 // 1
Pulmonary valve stenosis	0 // 2	1 // 1
Persistent ductus arteriosus	0 // 1	1 // 0
Other diagnosis*	55 // 0	55 // 0
Total	189 // 16	200 // 5

*, aortic valve stenosis, ventricular septal defect, aortic valve insufficiency, complete AV septal defect, congenitally corrected transposition of the great arteries, pulmonary atresia, double outlet right ventricle (TGA type), truncus arteriosus communis, double outlet right ventricle (Fallot type), persistent foramen ovale, mitral valve insufficiency, mitral valve prolapse, aortic aneurysm.

Table 6 Number of patients under medication at different observation times

Medication	During hospital stay	At the end of rehabilitation	After rehabilitation
	n (%)	n (%)	n (%)
Currently no medication	11 [5]	6 [3]	37 [18]
Primary cardiac drugs			
• Diuretics	135 [66]	148 [72]	77 [38]
• ß-Blockers	71 [35]	148 [72]	90 [44]
• ACE inhibitors	21 [10]	27 [13]	28 [14]
• Amiodarone	12 [6]	20 [10]	10 [5]
• Digitalis glycosides	8 [4]	13 [6]	11 [5]
• Antiarrhythmics, other	5 (2.5)	3 (1.5)	3 (1.5)
• AT-Blocker	4 [2]	8 [4]	5 (2.5)
• Ca-Antagonists	2 [1]	3 (1.5)	2 [1]
Anticoagulants			
• Anticoagulants, oral	74 [36]	106 [52]	65 [32]
• Platelet inhibitors	12 [6]	10 [5]	10 [5]
Primary non-cardiac drugs			
• Thyreoid hormones	29 [14]	39 [19]	41 [20]
• Antihyperlipidemic agents	5 (2.5)	7 (3.5)	8 [4]
• other*	94 [46]	122 [60]	85 [41]
No information	39 [19]	0	8 [4]

*, others: Proton pump inhibitors, Antihistamines, Antiepileptics, Allopurinol, Antidepressants, Contraceptives, Analgetics, Antibiotics, Benzodiazepine, Glucocorticoids, Minerals/Vitamins. ACE, angiotensin-converting-enzyme; AT, angiotensin; Ca, calcium.

Out of the six patients, who were "unable to work" at the end of the rehabilitation measures, three [Ebstein's anomaly (n=2), aortic valve insufficiency (n=1)] returned to work again and one patient retired.

Discussion

For the first time, the present study provides comprehensive data on the medical rehabilitation of ACHD after previous treatment in a tertiary care center.

The reason for conducting the present study was that despite the increasing number of ACHD worldwide, there are only few structured cardiological rehabilitation programs and few scientific studies on this specific patient population. In contrast, rehabilitation measures for acquired heart disease have been scientifically better investigated. The currently available data on ACHD derive mostly from small, uncontrolled studies with very different types of CHD, due to the fact that until a few decades ago the need for specific rehabilitation of patients with CHD was underestimated (16).

Current study data show that rehabilitation of ACHD requires consideration of special features that differ considerably from those of acquired heart disease. The fact that ACHD often cannot be treated in the same way as acquired heart disease places tremendous demands on rehabilitation facilities.

The data from a large cohort of native, surgically or interventional treated CHD (n=205), which included almost all types and severity degrees [moderate: 35.1% (n=72); severe: 41.0% (n=84)] of CHD and syndromes, showed that many of these patients required medical rehabilitation. Almost all patients (98.6%; n=202) had received up to six re-operations or an interventional treatment (26.8%; n=41) because of their CHD. The age of the included patients was low (median 31 years; range: 16 and 68 years) compared to

Table 7 Cardiac interventions after rehabilitation measures

Cardiac diagnosis	Sex, m/f	Age (years)	Interventions after rehabilitative measures
Aortic valve stenosis	M	16	Pacemaker implantation
Atrial septal defect	F	61	Pacemaker implantation
Double outlet right ventricle (Fallot type)	F	27	Stent implantation in RVOT
DORV-TGA	M	27	Additional RV-PM probe implantation
Ebstein's anomaly	F	32	Pacemaker implantation
Ebstein's anomaly	F	19	Amplatzer-ASD-Occluder
Pulmonary atresia + VSD	M	21	VSD closure
Pulmonary valve stenosis	F	29	PDA closure
Tetralogy of Fallot	M	65	Coronary stent
Tetralogy of Fallot	F	65	Pacemaker implantation
Tetralogy of Fallot	M	19	Stent implantation in RV-PA-Homograft and Melody valve
Tetralogy of Fallot	F	36	Pacemaker implantation
Tetralogy of Fallot	M	30	Stent implantation and implantation of a Melody valve
Transposition of the great arteries	F	34	ICD implantation
Transposition of the great arteries	M	36	MV replacement, TV-plastic, MV exchange, pacemaker revision
Transposition of the great arteries	M	29	Tricuspid valve occlusion occlusion
Tricuspid atresia	F	36	Coil closure of veno-venous collaterals
Tricuspid atresia	M	43	Pacemaker implantation
Truncus arteriosus communis	M	26	Balloon dilatation of the pulmonary artery + stent implantation (pulmonary artery)

M, male; F, female; RVOT, right ventricular outflow tract; DORV-TGA, double outlet right ventricle - transposition of the great arteries type; RV, right ventricle; PM, pacemaker; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; PA, pulmonary artery; ICD, implantable cardioverter-defibrillator; MV, mitral valve; TV, tricuspid valve.

the age of patients who normally receive rehabilitation due to acquired heart disease.

Although the majority of CHDs were "repaired" in the current study, almost all patients exhibited anatomical and/or functional conditions, residuals and sequelae. These conditions are typical for the pathological anatomy of the CHD or the type of therapeutic intervention and may have a negative impact on the quality of life, performance, work capacity and longevity. This situation also reflects the future requirement of modern rehabilitation facilities. Expectations placed on physicians and nursing staff of a rehabilitation clinic will be increasing in order to provide highly-qualified medical care.

One reason for the rising demand is the fact that the duration of the hospital stays of ACHD after cardiac operations or interventions or cardiac decompensation is becoming shorter and shorter. In addition, post-operative/interventional complications frequently occur in the first weeks and months after a hospital stay, i.e., during the period of rehabilitation. Therefore, physicians and nurses in rehabilitation facilities must be familiar with CHD and technically knowledgeable about how to manage specific complications.

Since CHD patients' rehabilitation needs are often complex, rehabilitation should preferably be performed in an experienced facility with an ACHD-certified (pediatric) cardiologist and in close cooperation with a supra-regional ACHD-center that can also provide multidisciplinary treatment of non-cardiac ACHD problems (6,17,18).

The use of rehabilitation facilities is further complicated by the fact that therapy goals for successful rehabilitation are currently not sufficiently defined, only cursory guidelines

or recommendations exist, and there are no concrete instructions that cover the needs of the ACHD (18). In order to meet the needs of this specific patient population and to take the particularities of symptoms, residuals, complications and problems into account, the near-term development of a structure for the practical implementation of rehabilitation in ACHD is necessary.

The ultimate goal of these efforts is to provide better care for ACHD, maintain or improve their condition and performance through an optimized rehabilitation program and to effect reduced morbidity and mortality. Particular attention should be paid to similarities with and differences from established rehabilitation concepts in acquired cardiovascular diseases (e.g., coronary heart disease, acquired valve changes or cardiac arrhythmias).

All rehabilitation measures, which are partly identical to tertiary prevention, share the commonality that they are intended to alleviate the consequences of the disease, prevent a recurrence, and prevent the disease from worsening. Various measures are applied, which primarily aim to inform patients, educate them, and improve their physical performance.

Acute- and post-acute phase

In the rehabilitation of ACHD, a distinction between the acute and the post-acute phase has to be made. In the acute phase, as in acquired heart disease, a comprehensive initial diagnosis should be made, which takes into account the patient's medical history, examination findings, previous medical reports and medical findings, resting ECG, echocardiography, exercise ECG and laboratory findings. On the basis of this diagnosis, rehabilitation goals must be set and therapeutic measures prescribed. All therapeutic goals are worked out together with the patient and focus on risk stratification, performance assessment and identification of individual problems (13,19).

In the early rehabilitation period of ACHD, the detection of periprocedural (postoperative/postinterventional) conditions and complications, typical for the specific CHD, is of particular importance. From the patients included in this study it can be deduced that, in particular, ventricular dysfunction, heart failure, pulmonary hypertension or pulmonary vascular disease, cardiac arrhythmias, valve thromboses, thromboembolism, wound healing disorders, fever, post-thoracotomy syndromes, thoracic scaffold pain, anaemia (after intraoperative blood loss, haemolysis), neurological and neurocognitive deficits, and reactive depression or a psychosyndromes are relevant (20,21).

For the management of these patients, it is important to consider the particularities of CHD. In contrast to acquired heart disease, ventricular dysfunction and heart failure in ACHD often affect the right (subpulmonary) ventricle or a morphologically right systemic ventricle. The assessment and treatment of impaired hemodynamics depends largely on the type of CHD and the extent of a ventricular dysfunction which often already exists preoperatively.

As the current study data show, this condition particularly affects complex CHD with chronic pressure or volume stress, e.g., univentricular hearts (after Fontan surgery), transposition of the great vessels after atrial switch operation with a systemic right ventricle, as well as pulmonary vascular disease resulting from a primary left-right shunt or severe heart valve disease, e.g., after repair of a Tetralogy of Fallot (22-27). These patients often respond differently to therapeutic measures than patients with acquired heart disease do (25,27).

In these patients, it is often difficult to detect heart failure using standard or threshold values (e.g., echocardiography), as these may be specific for the type of CHD and may differ from the values for acquired heart disease (e.g., Fontan circulation, after atrial redirection or in congenitally corrected transposition).

In principle, the drugs commonly used in adult cardiology are also used for ACHD, although the specific characteristics of CHD must be taken into account (26-31). Nevertheless, there are many uncertainties regarding therapeutic measures since comprehensive data from controlled studies are lacking (32).

As the study also shows, cardiac arrhythmias, especially in complex CHD, often occur as atrial arrhythmias and less frequently as ventricular arrhythmias. Particularly susceptible are native or pre-operated patients with atrial septal defect, tetralogy of Fallot, transposition of the great arteries after atrial redirection, functionally univentricular heart after Fontan surgery or Ebstein's anomaly (33). In rehabilitation, the detection and treatment of early postoperative cardiac arrhythmias is, therefore, of great importance (4,34). Additionally, it should be known that supraventricular tachycardias are poorly tolerated and can cause decompensation or death, especially in complex CHD (e.g., after atrial inversion, in Fontan circulation, in cyanotic heart defects, in Eisenmenger's syndrome) (27).

The secondary goal of antiarrhythmic therapy is to reduce morbidity, maintain ventricular function and improve prognosis by preventing sudden cardiac death. Risk

stratification for sudden cardiac death is difficult in CHD and must be highly individualized. Rehabilitation measures should already set the course in the right direction, although the treatment of complex CHD in particular should be reserved for specialists due to the special features typical of the underlying CHD (33-35).

Pulmonary arterial hypertension in ACHD particularly affects shunt lesions (with the extreme form of Eisenmenger's syndrome), congenital obstructions of the left heart, cyanotic heart disease with increased pulmonary flow, anomalies of the pulmonary artery and, more recently, patients with univentricular heart and Fontan circulation who develop pulmonary vascular disease (36-40).

Also in these patients, the therapy performed has to take the peculiarities of the CHD into account. The use of specific measures and highly effective, but not harmless drugs for pulmonary hypertension treatment, should be coordinated by specialists (26,27,36,39,41) This coordination is particularly true for patients with Eisenmenger's syndrome (42). Supportive therapy measures include treatment with diuretics, oxygen, oral anticoagulants, phlebotomies and compensation for anemia and/or iron deficiency (41,43). Drugs with systemic vasodilation (e.g., AT blockers, ACE inhibitors) are only applicable in special circumstances, but may also be contraindicated if they amplify an existing right-left shunt and a consecutive deepening of cyanosis. Of particular importance is the specific pharmacotherapy with endothelin antagonists, PDE-5 inhibitors, sGC stimulators, prostanoids, or IP prostacyclin receptor agonists which can significantly improve quality of life and prognosis (39).

In ACHD, special attention must be paid after a recently performed surgery. It is important to note that anaemia in vitally-associated cyanosis is defined, weighted and treated differently than in acquired heart disease (43).

Other common early postoperative/interventional problems concern the detection, evaluation and treatment of newly-occurring or persistent fever and inflammatory reactions (leukocytosis, increase of CRP, SPA, pro-calcitonin, etc.), as seen, for example, in endocarditis early after valve replacement or in wound infections and wound healing disorders. In principle, however, the diagnosis and treatment do not differ significantly from the postoperative procedures for acquired heart defects (44).

For endocarditis prophylaxis, the physician in the rehabilitation clinic must be aware of the special features of ACHD since the incidence of infective endocarditis is higher than in the general population (45,46). Since the mortality rate of the disease is still high and patients are at risk of developing infective endocarditis during rehabilitation, the rehabilitation clinic should be informed about typical symptoms (e.g., fever, night sweats, unclear weight loss, changed findings during auscultation, newly occurring heart failure) and patients should be advised about the necessity and practical implementation of endocarditis prophylaxis.

Rehabilitation in the post-acute phase

In ACHD, advice in the post-acute phase should include somatic, educational, psychological and social areas. The somatic area also includes the agreement of rehabilitation goals and the prescription of therapeutic measures (13,19).

Education should include health promotion and patients should be instructed about the importance of a healthy lifestyle. This lifestyle instruction includes the elimination of nicotine, the acquisition and adherence to a healthy diet, targeted necessary weight reduction and physical exercise. In addition, rehabilitative training is provided as required, e.g., on heart disease, endocarditis prophylaxis and, if necessary, self-management of oral anticoagulation.

Psychosocial support

The current study has shown that the somatic recovery and professional-/social integration of the often quite young patients depends largely on psychological and social factors. ACHD should be supported in the social field, in their professional reintegration as well as in their private environment (e.g., by drawing up a step-by-step reintegration plan and by initiating benefits for participation in working life) (47).

Mental stress often exerts a negative influence on the course of the illness. In some cases, neurological and neurocognitive deficits as well as reactive depression or psychosyndromes have existed since childhood (48). For this reason, screenings for post-traumatic stress disorder, depression, anxiety or social isolation should be included in the diagnostics at the beginning of rehabilitation measures by means of questionnaires and, if necessary, supplemented by individual interviews (13,49,50).

Physical exercise and resilience in ACHD

ACHD themselves often have limited knowledge about their heart defects, especially about their physical capacity

and the purpose/implementation of physical training (51).

Although it is known from patients with acquired heart disease and chronic heart failure that adapted aerobic endurance training can improve physical performance, reduce symptoms, improve quality of life and probably reduce morbidity and mortality, there is no reliable data for ACHD. Only small studies show that adapted, aerobic physical endurance training can improve physical performance and thus quality of life in ACHD through improved neurohumoral mechanisms and the adaptation of peripheral circulation. For this reason, rehabilitation measures should include a proposal for a specific training protocol after examining the patient's individual stress profile, which can and should be continued at home after discharge in order to improve resilience, well-being and other positive psychological changes (52).

In addition to the purely medical issues, a particular need exists for advice on disability and insurance law, old-age provision, forms of education (school, university, profession), earning capacity, obtaining a driving license, airworthiness and often also on pregnancy and inheritance of heart defects.

Health maintenance and prevention

Acquired co-morbidities, which occur frequently and have a lasting and unfavorable effect on the natural course of a CHD, are of particular relevance within a rehabilitation program for ACHD (53-55). In addition to acquired cardiovascular diseases (arterial hypertension, coronary heart disease, valvular diseases, endocarditis), this occurrence concerns the involvement of other organ systems, especially the lungs, pulmonary vessels, kidney, blood, coagulation system, central nervous system and metabolic disorders (diabetes mellitus, hyperlipidemia, hyperuricemia). Since ACHD are reaching an increasingly higher age, education about prevention of aggravation and complications as well as health promotion is paramount.

Final examination

The final examination includes a review of the drug therapy and the intended therapeutic goals, the preparation of an individual training plan for the time after rehabilitation, recommendations for further treatment (including medical check-ups, laboratory values, echocardiography) and the prescription of follow-up and preventive measures (e.g., in the outpatient coronary-sport groups, physiotherapy). In addition, the socio-medical classification is discussed with the patient (including restrictions on benefits and remaining positive performance) (49).

Limitations

Among the strengths of the current study are the large sample size of the patients and the inclusion of all types and severity degrees of CHD. This study has limitations as the study design was retrospective, therefore, no control group exists. The study was conducted at a tertiary center for adults with CHD and at a rehabilitation clinic specialized in ACHD. As a result, the distribution of patients in terms of type and severity of the underlying heart defect does not correspond to the typical patient population as seen by a general practitioner, internist or cardiologist. The prevalence of complex abnormalities is probably much higher in these facilities than in regional hospitals or in regular cardiology departments. The data presented is derived solely from patients living in Germany. The generalization of the conclusions and the transfer to patients living in other countries or different ethnic groups is debatable. Further studies are also required in this respect.

Conclusions

With the primary goal of reducing cardiac morbidity and mortality, cardiac rehabilitation and prevention programs for ACHD are an essential part of health care. Rehabilitation and prevention measures should include the reduction of typical and known cardiovascular risk factors as well as social and occupational reintegration. However, the difference between congenital and acquired heart disease must always be considered and not all measures applied to acquired heart disease can be transferred to ACHD.

The existing, rather modest data on rehabilitation and prevention in congenital heart disease need to be expanded. Randomized controlled studies on rehabilitation measures are necessary to prove the efficiency of follow-up treatment and to develop concepts specific to CHD.

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5 Discussion

Few areas of modern medicine have seen as much success as the treatment of CHD (31). Through advances in modern cardiac surgery, (pediatric) cardiology, intensive care, and pharmacotherapy, in the industrialized world, up to 97% of patients with congenital heart defects of all severities reach adulthood (88). The number of ACHD has expanded to such an extent that it now exceeds the number of children with CHD, and many of these ACHD are sufficiently resilient, with adequate QoL and subjective feelings of wellness (15, 89).

Nevertheless, all patients with CHD are and will remain in a state of health instability due to their heart defect (22, 35, 37). Even if treated surgically or interventionally, the CHD is never cured; it may be palliated or at best repaired, but still requires lifelong follow-up due to several residua and sequalae (19, 22, 27). In addition, although their importance has been underestimated for a long time, non-cardiac comorbidities play a major role in ACHD care. Neidenbach et al. (26) found in a large cohort of several hundred ACHD that 95% had concomitant cardiac and non-cardiac disease(s). This finding was also supported by Singh et al. (90) in a large contemporary study of ACHD hospitalizations from the US National Inpatient Sample Database. Overall, adequate, life-long, specialized healthcare, provided by experienced ACHD specialists, is one of the most important determinants of well-being and long-term survival in ACHD (3, 22, 35, 91). Unfortunately, such care is currently not the norm; neither in Germany, nor in most other countries around the world (38-40).

In contrast to acquired heart disease, there are still several major uncertainties and management gaps in (A)CHD, particularly regarding sex/gender differences, aortopathies, and rehabilitation measures.

This dissertation describes these previously rather ignored aspects in the context of the current health status of ACHD. In order to provide ACHD with adequate and innovative healthcare in the future, the author:

(I) elucidated patient-reported sex/gender differences concerning healthcare status, current healthcare availability, counselling needs, and QoL;

(II) acquired real world data on the health status of patients and the provision of health services by PCPs for ACHD with aortic abnormalities;

(III) obtained comprehensive primary data on specific needs of ACHD requiring rehabilitation measures to develop a concept for the implementation of such measures.

In *Article 1* as well as in *Article 2,* it was shown that, for most ACHD (up to 90% of all included patients), the PCP was the first to be consulted for general medical problems, regardless of the patient's diagnosis, the severity and complexity of the CHD, or gender. PCPs were mostly also the primary contact in cases of medical problems related to the patients' CHD.

The PCPs were usually well informed about the presence of a CHD in their patients. Nevertheless, many PCPs, and also patients, were unaware that CHD is a chronic health condition necessitating life-long follow-up and sometimes repeated interventions and re-operations. Many PCPs had no clinical experience with long-term problems in the course of a specific CHD, which can be critical, particularly in CHDs with aortic involvement (35, 92). This is a major problem, as in the German healthcare system, the PCP could and should be the gatekeeper for adequate patient management, and should regularly draw his patients' attention to obligatory ACHD check-ups. However, as both surveys show, only slightly more than half of the ACHD had ever been referred to a specialized ACHD institution. The results of a recently published study fit in well with this, demonstrating that less than 25% of PCPs in Germany involve ACHD-specialized physicians in the follow-up of their adult patients with CHD (35).

When PCPs refer ACHD for further cardiological care, it is usually to general cardiologists, but in most cases these physicians are also not specifically trained to treat ACHD. PCPs and general cardiologists must bear in mind that the cardiac and non-cardiac problems in ACHD may differ significantly from those in patients with acquired heart disease. The diagnosis and management of these medical problems, as well as their timely and correct detection, is essential.

Unlike other, small studies on sex/gender differences (4, 12, 48), *Article 1* used PROMs to asses sex/gender differences regarding cardiac diagnosis, health condition, comorbidities, health care details, individual counselling needs, and QoL. As described in the literature, female patients tend to have rather simple shunt lesions (52, 53), while male patients have more complex/severe CHD (50) and show a higher preponderance of aortic involvement (7, 51). In our current study, significant differences were also observed, including female predominance in TOF, ASD, and PDA, and male predominance in aortic valve stenosis/insufficiency and TGA. Even though no clear explanation exists for these imbalances, an effect of sex on the natural course of the CHD cannot be disregarded (51). Although CHD is thought to be genetically determined, so far only a few genes linked to the occurrence of CHD have been identified. Therefore, in addition to genetic factors, environmental influences are likely to be at least partially responsible for CHD (54). On the other hand, differences could also reflect CHD birth prevalences (58).

According to the presented data, significantly more men than women primarily consulted their PCP rather than a CHD specialist if a problem associated with the CHD was suspected. This observation corresponds with recent findings that men in general tend to prefer to visit their PCP, while women prefer specialists (93).

Both sexes had a high need for counselling, but there were significant differences between male and female participants. In terms of QoL, female participants reported greater impairments, especially in everyday activities, more pain/physical complaints, and more anxiety/depression. Because these data are fairly recent, this suggests that PCPs, who are typically the first responders for medical questions, as well as ACHD specialists, need a better understanding of the importance of gender differences in ACHD.

Despite all efforts, data from the literature also indicate that in the long term, further sex/gender-sensitive research on ACHD is needed, particularly regarding cardiovascular complications, acquired comorbidities, and psychosocial support. As already shown in *Figure 7*, women have a 33% lower risk of aortic complications (e.g., aneurysms, dissection, and need for operation), a 47% lower risk of infective endocarditis, a 12% lower risk of relevant arrhythmias, and a 55% lower need for implantation of a cardioverter defibrillator (ICD) (50, 51, 94). However, with the exception of PH, all ORs mentioned should be scrutinized more closely in the future. For example, current studies show that female ACHD report symptoms of cardiac arrhythmias more often than male ACHD do (50, 51).

As patients with CHD get older, sex-specific differences regarding acquired comorbidities become more relevant. As is known from acquired heart disease, the incidence of neurological events usually increases in women with advancing age, often resulting in more serious consequences than in men (95). Women also tend to develop coronary artery disease up to ten years later than men (96). Future studies will show whether these sorts of differences also apply to ACHD.

The psychological needs of ACHD have recently received increased attention (30, 97-100). Nevertheless, there have been no sex/gender-specific studies on mental stress in ACHD. It is therefore the task of future psychological/clinical studies to clarify whether psychological problems actually occur more frequently in women or whether gender-specific social/role expectations distort the results. Also, mortality and long-term survival after different interventions or operations between the sexes is controversial. Taking into account that male ACHD tend to have more severe CHD, the cumulative surgical risk is higher in men. Therefore,

overall mortality is also higher in male ACHD, resulting in better long-term survival in female ACHD (50, 58, 59).

In addition to the described clinically relevant parameters - which predominantly refer to biological sex - attention should also be paid to sociocultural sex, especially in real-life care and with respect to psychosocial demands (100). The perceived gender role appears to be an important determinant of disease perception, affecting an individual's behavior. The traditional male gender role implies rational, achievement-oriented, and demanding behavior with help-seeking behavior indicating weakness. The traditional female gender role, in contrast, implies stronger social integration, and as a result, a greater acceptability of help-seeking behavior (101). Therefore, gender role typically affects the way patients cope with a cardiac disease (102), and thus affects counselling needs. The Canadian MHART study (103) even showed that, as a consequence of gender differences, different forms of psychosocial treatment are advisable.

Regarding QoL, women are more likely to report an overall poorer QoL (104). This also appears to be the case for ACHD. In an Asian study of QoL in ACHD, female sex was associated with poorer physical and psychosocial functioning (105). Although the underlying mechanism remains unclear, it seems plausible that the results are more related to gender-specific psychosocial factors, such as personality traits, distress, and family support, rather than biological sex per se (84).

As described in *Article 2*, a considerable percentage (26.3%) of the included ACHD had a manifest aortopathy, and an additional 13.1% were at risk of developing an aortopathy in the long term. In the presented cohort, significantly more men than women had aortic involvement in their CHD. As already mentioned, no causality underlying this difference has yet been found, although genetics seems to be responsible for the male preponderance in aortic disease (106). Differences could also reflect the extent to which CHD prevalence at birth is known, as men are more likely than women to have more severe CHD (58).

Clinically relevant is the fact that aortopathies are often overlooked, may progress, and may put the affected patients at risk for devasting complications, such as aortic aneurysm formation or aortic dissection or rupture. In order to prevent these complications, identifying high-risk patients at an early stage and, if necessary, treating them prophylactically or providing them with appropriate surgical or sometimes interventional treatment in a timely manner is critical. Therefore, it is important to mention that the decision-making process is strongly dependent on the underlying CHD. Unfortunately, guidelines for prophylactic strategies in adults with

acquired, degenerative forms of aortic aneurysm only apply to a limited extent to aortopathies in CHD. In this regard, one of the most important and alarming observations was that nearly half of the ACHD were unaware of the availability of specialized care, such as ACHD-certified adult and pediatric cardiologists, regional ACHD facilities, and tertiary ACHD care centers. As these information deficits exist not only among patients, but also among their PCPs (35), it is essential to increase awareness of ACHD-specialized institutions, both for patients and their referring physicians. In this context, it is concerning how high the demand for consultation among ACHD was. The majority of ACHD had a deep need for counseling, especially with regard to exercise capacity, daily life, pregnancy, insurance issues, and also rehabilitation measures.

However, to advise ACHD on these issues, health care professionals require a great deal of expertise and experience, often going far beyond the competence of a generally trained PCP or general cardiologist, particularly in complex ACHD. Due to the complexity of many CHD, and the high variability in heart defect-specific characteristics, this can only be achieved holistically by specialists within the framework of multidisciplinary care (27, 35, 37). Only these highly experienced specialists are in a position to make competent decisions regarding prophylactic recommendations and therapeutic recommendations on conservative, surgical, or interventional procedures for ACHD with an aortopathy.

Their specific advice, which is strongly dependent on the underlying disease, should cover specific prophylactic or therapeutic measures to prevent the progression of aortic dilatation (107). The main long-term aim is to reduce the risk of serious complications such as aortic dissection or rupture. Such information can be obtained by the PCP only if collaboration with specialists is enhanced. Affected patients should be instructed to avoid physically demanding sporting activities or those with an increased risk of injury, while moderate, low-dynamic endurance exercise with avoidance of static loads, such as cycling, is advisable. For medical prophylaxis to protect against the progression of aortic widening, for example, data are available for patients with Marfan syndrome, but not for those with aortopathies associated with other forms of CHD. In general, disproportionate increases in blood pressure or aortic wall tension should be reduced. Options for prophylaxis or treatment consist mainly of pharmacologic aortic protection (e.g. by beta-blockers or AT-blockers) as well as the timely indication for prophylactic aortic root replacement (107).

In this context, it must be emphasized that the indication for prophylactic surgery in adults with acquired, degenerative forms of aortic aneurysm can only be applied to a limited extent to aortopathies in CHD (108-110). It should also be noted that aortic dilatation and the resulting

increased aortic stiffness can also lead to progressive aortic valve regurgitation, left ventricular hypertrophy, reduced coronary artery flow, and left ventricular failure in the long term (41, 108-111).

Appropriate consultation is also required regarding pregnancies in the above-mentioned patient groups, because of the hormonally induced risk of aortic dissection during or even after pregnancy and delivery (31). For this consultation, PCPs should refer patients at risk to specialized centres throughout their pregnancy.

Article 3 demonstrates that rehabilitation in ACHD was safe and the outcomes favorable. Overall, functional class improved, cardiac medication could often be reduced, work capability increased, and cardiovascular risk factors could be addressed.

All ACHD, including patients with aortopathy developing within the natural course of the disease or after aortic surgery, can benefit from appropriate rehabilitation measures (72). In Germany, rehabilitation is offered for adults with genetically determined aortic disease that is similar to a Norwegian model (112, 113). Therefore, rehabilitation refers not only to the cardiovascular system, but also to living with hereditary disease in general (113).

However, study data show that ACHD often cannot be approached in the same way as patients with acquired heart disease. Almost all ACHD exhibit anatomical and/ or functional conditions, residua, and sequelae that have the potential to negatively impact QoL, general performance, work capacity, and longevity. The described study results also reflect the need for a future requirement for ACHD rehabilitation. Expectations placed on physicians and nursing staff of a rehabilitation clinic should increase in order to provide highly qualified medical care. One reason for the rising demand is the fact that the duration of hospital stays of ACHD after cardiac operations or interventions, or cardiac decompensation, is becoming increasingly shorter. In addition, if post-operative or post-interventional complications occur, it is usually in the first weeks and months after hospital discharge, i.e. during early rehabilitation. Therefore, physicians and nurses in rehabilitation facilities must become familiar with CHD and specific potential complications.

Our study results indicate that rehabilitation should preferably be performed in an experienced facility with an ACHD-certified congenital cardiologist, and in close cooperation with a supra-regional ACHD center that can provide multidisciplinary treatment of non-cardiac ACHD problems, if needed (27, 32, 72, 80). A recent meta-analysis by Bathen et al. (112) of rehabilitation measures for hereditary aortic disease has shown that it is particularly important

to pursue a multidisciplinary, holistic treatment approach. This is also applicable to ACHD, especially with regard to patient satisfaction and psychological well-being (114-116). The utilization of rehabilitation facilities is further complicated by the fact that in ACHD, therapeutic goals for successful rehabilitation are currently not sufficiently defined. Only cursory guidelines or recommendations exist, and there are no concrete instructions that cover the needs of the ACHD (80).

The current study data specifically characterize the needs of this patient population, as well as details on their symptoms, residua, sequelae, complications, and comorbidities. Therefore, the near-term development of a specialized facility for rehabilitation in ACHD is necessary. Particular attention should be paid to similarities with and differences from established rehabilitation concepts in acquired cardiovascular disease.

In addition, sex/gender-specific characteristics, as described in *Article 1*, should also be considered for the future design of rehabilitation measures and guidelines. Although no sex/ gender-specific studies on rehabilitation in ACHD have been conducted to date, women and men may equally profit from cardiac rehabilitation (117). However, biological and social differences should be taken into account, as gender-sensitive rehabilitation measures might differ in risk profile, morbidity, treatment, and outcome (35, 37, 41, 84, 87, 118).

The extensive data collected enables the proposal of practical recommendations for the rehabilitation process in ACHD, as follows.

In the medical rehabilitation process of ACHD, a distinction has to be made between the acute and the post-acute phase. In the acute phase, as in acquired heart disease, a comprehensive initial diagnosis should be made, taking into account the patient's medical history, clinical examination results, and ECG, echocardiography, imaging, and laboratory findings. Rehabilitation goals must be set, and therapeutic measures chosen, based on these data. All therapeutic goals should be elaborated together with the patient, focusing on risk stratification, performance assessment, and identification of individual problems (73, 76). In particular, ventricular dysfunction, heart failure, pulmonary hypertension or pulmonary vascular disease, cardiac arrhythmias, valve thromboses, thromboembolism, wound healing disorders, fever, post-thoracotomy syndromes, thoracic scaffold pain, anaemia (after intraoperative blood loss, haemolysis), neurological and neurocognitive deficits, and reactive depression or psychosyndromes all have to be considered (20, 23, 111, 119).

In the post-acute phase, advice for ACHD should cover somatic, educational, psychological, and social areas. The somatic area also includes the delineation of rehabilitation goals and the prescription of therapeutic measures (73, 76). Education should include health promotion and patients should be instructed about the importance of a healthy lifestyle. These lifestyle instructions include the elimination of nicotine, the acquisition and adherence to a healthy diet, targeted necessary weight reduction, and physical exercise. In addition, special teaching is provided, e.g. on heart disease, endocarditis prophylaxis, and, if necessary, self-management of oral anticoagulation.

Somatic recovery and professional/social integration in often quite young adults depends largely on psychological and social factors. ACHD should be supported in the social field; in their professional reintegration as well as in their private environment, e.g., by drawing up a step-by-step reintegration plan and by initiating benefits for participation in working life (120). Mental stress often exerts a negative influence on the course of the illness. In particular cases, neurological and neurocognitive deficits as well as reactive depression or psycho-syndromes may exist (21). For this reason, screenings for post-traumatic stress disorder, depression, anxiety, or social isolation should be included in the diagnostics at the beginning of rehabilitation, measured by means of questionnaires, and, if necessary, supplemented by individual interviews (73, 76, 121).

ACHD must be informed about their heart defects, especially about their physical capacity and the purpose/implementation of physical training (22, 31). It must be remembered that, although adapted aerobic endurance training can improve physical performance, reduce symptoms, improve QoL, and probably reduce morbidity and mortality in patients with acquired heart disease and chronic heart failure, reliable data for ACHD are missing (122). For this reason, rehabilitation measures for ACHD should include a proposal for a specific training protocol according to the patient's individual stress profile, which can and should be continued at home after discharge in order to improve resilience, well-being, and other positive psychological changes (123).

In addition to the purely medical and psychological issues, a particular need exists for advice on disability and insurance law, old-age provision, forms of education (school, university, and professional), earning capacity, obtaining a driving license, fitness to fly, and often also on pregnancy and inheritance of heart defects (22, 31, 35, 37). Acquired comorbidities, which occur frequently and have a lasting and unfavorable effect on the natural course of CHD, should be considered within a rehabilitation program for ACHD (25, 124-126). In addition to acquired cardiovascular diseases, such as arterial hypertension, coronary artery disease,

valvular heart diseases, and endocarditis, this occurrence concerns the involvement of other organ systems, especially the lungs, pulmonary vessels, kidneys, blood, coagulation system, central nervous system, and metabolic disorders (e.g., diabetes mellitus, hyperlipidemia, or hyperuricemia) (124, 125, 127). Since ACHD are reaching an increasingly higher age, education about prevention of aggravation and complications as well as health promotion is paramount.

The post-acute phase and also the entire rehabilitation should be concluded with a final review addressing the patient's current drug therapy and intended future therapeutic goals, the preparation of a post-rehabilitation individual training plan, recommendations for further treatment (including medical check-ups, laboratory values, and echocardiography) and the prescription of follow-up and preventive measures (e.g., outpatient CHD sport groups or physiotherapy) (87, 120).

6 Conclusion and Future Aspects

For many years, CHD in adults was the most neglected area of modern cardiology (27). Although this situation has improved, the results of the presently described studies show that there are still major deficits and research gaps in the medical care of ACHD in Germany, and probably also in the entire world.

As illustrated by the three published research studies presented in this dissertation, future state-of-the-art health care for ACHD requires better education and awareness of ACHD-specific issues and the tremendous importance of lifelong follow-up, by PCPs, ACHD healthcare providers, and ACHD themselves. Routine follow-up by experienced, specialized and/or certified physicians or centers is imperative for all patients with CHD, including those with intrinsic aortopathy or at risk for aortopathy.

Consideration of sex/gender differences in diagnosis, pathogenesis, pharmacokinetics, therapy, prognosis, long-term outcome, disease prevention, and medical rehabilitation will be critical to the development of optimal treatment strategies for individual ACHD. In the long term, relevant guidelines should be developed for gender-specific disease management in ACHD.

Although there are significant adverse effects on morbidity and mortality, aortopathy is a frequently overlooked condition in ACHD. As aortopathy becomes more important with increasing age and complexity of CHD, both patients and treating physicians need to be better educated about aortopathies and the potential associated risks. Furthermore, Lammers et al. (128) propose a departure from the paternalistic doctor-patient paradigm, and the development, in its place, of a modern marketing approach that views patients as customers and rational individuals.

Regarding rehabilitation measures, the study presented here provides, for the first-time, comprehensive data on the course of rehabilitation in a large cohort of ACHD after surgical or interventional treatment. Overall, the outcomes for ACHD after rehabilitation were uneventful and favorable. Further research is required to assess long-term clinical outcomes and the impact of rehabilitation on QoL, disease coping, and employment. The results of this study can serve as a benchmark for the development of specific rehabilitation programs for ACHD.

As the presented data derive from people living in Germany, further studies are needed to assess the status of CHD patient care in other countries. Because of the increasing number of ACHD, in a next step, further data could be collected from other countries for comparison purposes in order to establish practical ACHD-specific international medical rehabilitation guidelines. Further research is needed to fill the existing research gaps regarding gender differences, aortopathies, and rehabilitation measures for ACHD (41, 84, 87).

Finally, for future patient management, precision medicine needs to be developed and focused on ACHD, integrating new insights into interactions between the genome, phenome, and environome, which will require complementary use of new technology, especially telemedicine, machine learning, and the use of Big Data (16, 129-131)

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Appendix

VEmaH Patient Questionnaire

Information

Sehr geehrte Patientinnen, Sehr geehrte Patienten!

wir bitten Sie herzlich, an einer wissenschaftlichen Untersuchung der Klinik für angeborene Herzfehler und Kinderkardiologie des Deutschen Herzzentrums München i teilzunehmen.

Dieser Fragebogen untersucht die **aktuelle Versorgungssituation von Erwachsenen mit angeborenen Herzfehlern (EMAH)**. Mit der Teilnahme leisten Sie einen sehr wichtigen Beitrag für die Versorgungsituation der Zukunft! Die Bearbeitung dauert maximal 10 Minuten!

Ihre Daten dienen ausschließlich zur statistischen Auswertung und zur Abfassung von wissenschaftlichen Publikationen. Sie erfolgt nach gesetzlichen Bestimmungen und setzt Ihre Einwilligung voraus.

Vielen Dank für Ihre Unterstützung!

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Einwilligungserklärung / Datenschutzerklärung gemäß Europäischer Datenschutz-Grundverordnung (DSGVO)[1]

Im Rahmen des Forschungsprojekts „Versorgungssituation von Erwachsenen mit angeborenen Herzfehlern (VEmaH)" soll die aktuelle Versorgungssituation von Erwachsenen mit angeborenen Herzfehlern (EmaH) untersucht werden. Alleinig für vorgenannten Forschungszweck sollen Daten durch das **Studienzentrum*** verarbeitet werden (Verarbeitung im Sinne von Erhebung, Speicherung, Veränderung und Nutzung).

Hierzu ist eine freiwillige und informierte Einwilligung erforderlich.
Die Datenerhebung erfolgt nicht personenbezogen. Das bedeutet, dass auf Grund der erhobenen Daten keine Rückschlüsse auf Sie gezogen werden können. Die Forschungsergebnisse werden in wissenschaftlich üblicher Form veröffentlicht. Wir sichern zu, dass aus den Veröffentlichungen keinerlei Rückschlüsse auf natürliche Personen möglich sind.

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Hiermit bestätige ich, dass ich diese Datenschutzerklärung gelesen und verstanden habe und unter diesen Bedingungen freiwillig am Forschungsprojekt „Versorgungssituation von Erwachsenen mit angeborenen Herzfehlern (VEmaH)" teilnehmen möchte.

....
Ort, Datum **Unterschrift**

[1] Verordnung (EU) 2016/679 des Europäischen Parlaments und des Rates vom 27. April 2016 zum Schutz natürlicher Personen bei der Verarbeitung personenbezogener Daten, zum freien Datenverkehr und zur Aufhebung der Richtlinie 95/46/EG (Datenschutz-Grundverordnung)

Beginn des Fragebogens

1. Ihr Alter: _____ Ihr **Geschlecht:** ❑ männlich ❑ weiblich Ihre **Postleitzahl:** _____

2. Sie **leben** in einer:
   - ❑ Großstadt (> 100.000 Einwohner)
   - ❑ Mittelstadt (> 20.000 – 100.000 Einwohner)
   - ❑ Kleinstadt (5.000 – 20.000 Einwohner)
   - ❑ Landgemeinde (< 5.000 Einwohner)

3. Welche Form von **angeborenen Herzfehlern** haben Sie?
   - ❑ Aortenisthmusstenose
   - ❑ Aortenklappenstenose/ Aortenklappeninsuffizienz
   - ❑ Atrioventrikulärer Septumdefekt
   - ❑ Fallot´sche Tetralogie
   - ❑ Hypoplastisches Linksherzsyndrom
   - ❑ Persistierender Ductus Arteriosus Botalli
   - ❑ Pulmonalklappenstenose/ Pulmonalklappeninsuffizienz
   - ❑ Transposition der großen Arterien
   - ❑ Univentrikuläres Herz
   - ❑ Ventrikelseptumdefekt
   - ❑ Vorhofseptumdefekt
   - ❑ Ich habe mehrere Herzfehler, nämlich: _____
   - ❑ Einen anderen Herzfehler, und zwar: _____

4. Leiden Sie an einer der folgenden **Erkrankung?**

Marfan - Syndrom	Ja ❑	Nein ❑	Weiß nicht ❑
Ehlers - Danlos - Syndrom	Ja ❑	Nein ❑	Weiß nicht ❑
Turner - Syndrom	Ja ❑	Nein ❑	Weiß nicht ❑
Morbus Fabry	Ja ❑	Nein ❑	Weiß nicht ❑

5. Leiden Sie unter einer der folgenden **typischen Begleit- oder Folgeerkrankungen Ihres Herzfehlers?**
   - ❑ Herzschwäche
   - ❑ Herzrhythmusstörungen
   - ❑ Herzinnenhautentzündung (Endokarditis)
   - ❑ Koronare Herzerkrankung
   - ❑ Veränderungen im Blutbild
   - ❑ Weiß nicht
   - ❑ Gerinnungsstörungen
   - ❑ Psychische Einschränkungen
   - ❑ Thrombosen
   - ❑ Lungenhochdruck
   - ❑ Neurologische Komplikationen
   - ❑ Nein, ich leide an keiner Begleit-/ Folgeerkrankung

6. Wer ist Ihr **erster Ansprechpartner bei allgemeinmedizinischen/gesundheitlichen Problemen**, die **nicht** in Zusammenhang mit Ihrem Herzfehler gebracht werden, und welche Fachrichtung hat dieser Arzt?
   - ❑ Allgemeinarzt
   - ❑ Praktischer Arzt
   - ❑ Internist
   - ❑ Eine andere Fachrichtung, und zwar: _____

7. Führt dieser niedergelassene Arzt auch eine **Zusatzbezeichnung**? Wenn ja, welche?
   - ❑ Kardiologie
   - ❑ Gastroenterologie
   - ❑ Hämatologie
   - ❑ Angiologie
   - ❑ Pneumologie
   - ❑ Endokrinologie
   - ❑ Rheumatologie
   - ❑ Nephrologie
   - ❑ Keine Zusatzbezeichnung
   - ❑ Weiß nicht
   - ❑ Eine andere Schwerpunktbezeichnung, und zwar: _____

8. Ist diesem **Arzt bekannt**, dass Sie einen **angeborenen Herzfehler haben?**
   - ❑ Ja ❑ Nein ❑ Weiß nicht

9. Wer ist Ihr erster Ansprechpartner bei Problemen in **Zusammenhang mit Ihrem angeborenen Herzfehler**, und welche **Fachrichtung** hat dieser Arzt?
   - ❑ Allgemeinarzt
   - ❑ Praktischer Arzt
   - ❑ Internist
   - ❑ Eine andere Fachrichtung, und zwar: _____

10. Führt dieser niedergelassene Arzt auch eine **Zusatzbezeichnung**? Wenn ja, welche?
    - ❑ Kardiologie
    - ❑ Gastroenterologie
    - ❑ Hämatologie
    - ❑ Angiologie
    - ❑ Pneumologie
    - ❑ Endokrinologie
    - ❑ Rheumatologie
    - ❑ Nephrologie
    - ❑ Keine Zusatzbezeichnung
    - ❑ Weiß nicht
    - ❑ Eine andere Schwerpunktbezeichnung, und zwar: _____

11. Handelt es sich bei dem Arzt, den Sie bei **allgemeinmedizinischen/gesundheitlichen Problemen** und bei **Problemen in Zusammenhang mit Ihrem angeborenen Herzfehler** aufsuchen, **um denselben Versorger?**
    ❑ Ja ❑ Nein

12. Welchen **Versicherungsstatus** haben Sie aktuell?
    ❑ Gesetzliche Krankenversicherung ❑ Private Krankenversicherung ❑ Keine ❑ Weiß nicht

13. Besteht aus Ihrer Sicht ein Bedarf an **spezifischer Beratung** für Patienten mit angeborenen Herzfehlern bezüglich folgender Themen?

Krankenversicherung	❑ Ja	❑ Nein	❑ Weiß nicht
Lebensversicherung	❑ Ja	❑ Nein	❑ Weiß nicht
Alterssicherung	❑ Ja	❑ Nein	❑ Weiß nicht

14. Welchen **Grad der Behinderung** haben Sie? _____ (in 10er Schritten von 0-100)

15. Besteht aus Ihrer Sicht der **Bedarf an spezifischer Beratung, vor allem** hinsichtlich **Behinderung und folgender Themen?**
    ❑ Ja, bezüglich Rente ❑ Ja, bezüglich Schwerbehindertenausweis ❑ Nein

16. Werden Ihnen regelmäßig **sehr teure Medikamente** verordnet?
    ❑ Ja, Medikamente wegen Lungenhochdruck ❑ Ja, Gerinnungshemmer ❑Nein
    ❑ Weiß nicht ❑ Sonstige, und zwar: _____

17. Hat Ihr Hausarzt **Probleme bei der Verordnung** Ihrer Medikamente? (z.B. auf Grund hoher Kosten?)
    ❑ Ja ❑ Nein ❑ Weiß nicht ❑ Ich nehme keine Medikamente

18. Bitte bewerten Sie mit Schulnoten Ihre aktuelle **Versorgungslage in Zusammenhang mit Ihrem Herzfehler!**
    ❑ Sehr gut ❑ Gut ❑ Befriedigend ❑ Ausreichend ❑ Mangelhaft ❑ Ungenügend

19. Bitte bewerten Sie mit Schulnoten Ihre aktuelle allgemeinmedizinisch-ärztliche **Versorgungslage!**
    ❑ Sehr gut ❑ Gut ❑ Befriedigend ❑ Ausreichend ❑ Mangelhaft ❑ Ungenügend

20. Besteht aus Ihrer Sicht ein **Bedarf an spezifischer Beratung** für Patienten mit angeborenen Herzfehlern bezüglich folgender Punkte? Wenn ja, bitte ankreuzen! (Mehrfachantworten möglich)
    ❑ Rehabilitationsmaßnahmen ❑ Bildungsformen (Schule, Studium, Beruf)
    ❑ Berufsfähigkeit ❑ Belastbarkeit im Alltag
    ❑ Führerscheinerwerb ❑ Flugtauglichkeit
    ❑ Leistungsfähigkeit, sportliche Betätigung ❑ Genetische Beratung
    ❑ Ernährung und Bewegung ❑ Prävention
    ❑ Schwangerschaft ❑ Sonstige, und zwar: _____

21. Ist Ihnen bekannt, dass es **zertifizierte Kliniken/ Zentren** für **Erwachsene mit angeborenen Herzfehlern** gibt? (Mehrfachantworten möglich)
    ❑ Ja, und zwar niedergelassene Kinderkardiologen mit EMAH-Zertifizierung
    ❑ Ja, und zwar niedergelassene Kardiologen mit EMAH-Zertifizierung
    ❑ Ja, und zwar zertifizierte EMAH-Schwerpunktkliniken, EMAH-Zentren
    ❑ Nein, mir sind keine zertifizierten Kliniken/Zentren für EMAH bekannt

22. Hat Sie Ihr niedergelassener Arzt in der **Vergangenheit** an eine **EMAH-zertifizierte Institution** überwiesen?
    ❑ Ja, bei kardialen Probleme in Zusammenhang mit meinem Herzfehler
    ❑ Ja, bei Problemen/ Erkrankungen, deren Verlauf von meinem Herzfehler beeinflusst werden kann
    ❑ Nein, ich wurde noch nie in eine EMAH-Institution überwiesen

23. Sind Sie über die **spezifischen Versorgungszentren ausreichend informiert?**
    ❑ Ja ❑ Nein ❑ Weiß nicht

24. Sind Ihnen **Selbsthilfeorganisationen für EMAH** bekannt? (z.B. Bundesverband JEMAH e.V., Deutsche Kinderherzstiftung, Bundesverband herzkranker Kinder e.V., Herzkind e.V.)
    ❑ Ja ❑ Nein ❑ Weiß nicht

25. Sind Sie bereit an einer vertiefenden **Befragung** teilzunehmen?
    ❑ Ja, bitte **kontaktieren Sie mich** unter folgender Emailadresse: _____
    ❑ Nein danke, ich bin an einer Befragung nicht interessiert

Bitte füllen Sie im Anschluss 5 Fragen zur Lebensqualität aus!

Bitte **kreuzen** Sie unter jeder Überschrift DAS Kästchen an, das Ihre Gesundheit HEUTE am besten beschreibt.

BEWEGLICHKEIT / MOBILITÄT

Ich habe keine Probleme herumzugehen ❑
Ich habe leichte Probleme herumzugehen ❑
Ich habe mäßige Probleme herumzugehen ❑
Ich habe große Probleme herumzugehen ❑
Ich bin nicht in der Lage herumzugehen ❑

FÜR SICH SELBST SORGEN

Ich habe keine Probleme, mich selbst zu waschen oder anzuziehen ❑
Ich habe leichte Probleme, mich selbst zu waschen oder anzuziehen ❑
Ich habe mäßige Probleme, mich selbst zu waschen oder anzuziehen ❑
Ich habe große Probleme, mich selbst zu waschen oder anzuziehen ❑
Ich bin nicht in der Lage, mich selbst zu waschen oder anzuziehen ❑

ALLTÄGLICHE TÄTIGKEITEN *(z.B. Arbeit, Studium, Hausarbeit, Familien- oder Freizeitaktivitäten)*

Ich habe keine Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
Ich habe leichte Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
Ich habe mäßige Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
Ich habe große Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
Ich bin nicht in der Lage, meinen alltäglichen Tätigkeiten nachzugehen ❑

SCHMERZEN / KÖRPERLICHE BESCHWERDEN

Ich habe keine Schmerzen oder Beschwerden ❑
Ich habe leichte Schmerzen oder Beschwerden ❑
Ich habe mäßige Schmerzen oder Beschwerden ❑
Ich habe starke Schmerzen oder Beschwerden ❑
Ich habe extreme Schmerzen oder Beschwerden ❑

ANGST / NIEDERGESCHLAGENHEIT

Ich bin nicht ängstlich oder deprimiert ❑
Ich bin ein wenig ängstlich oder deprimiert ❑
Ich bin mäßig ängstlich oder deprimiert ❑
Ich bin sehr ängstlich oder deprimiert ❑
Ich bin extrem ängstlich oder deprimiert ❑

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- 100 ist die beste Gesundheit, die Sie sich vorstellen können.
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- Bitte kreuzen Sie den Punkt auf der Skala an, der Ihre Gesundheit HEUTE am besten beschreibt.
- Jetzt tragen Sie bitte die Zahl, die Sie auf der Skala angekreuzt haben, in das Kästchen unten ein.

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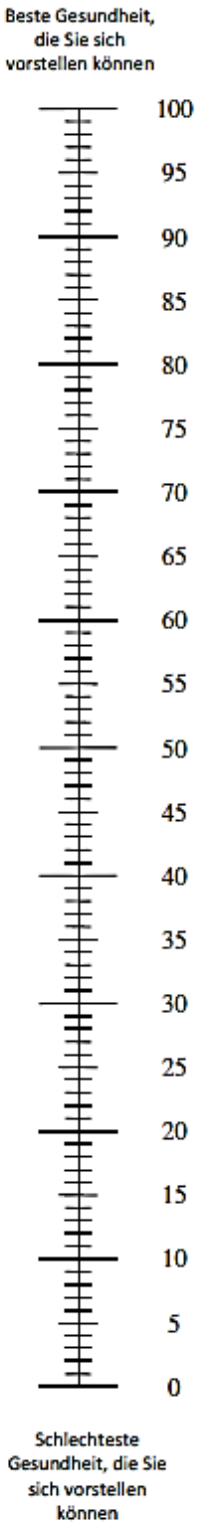

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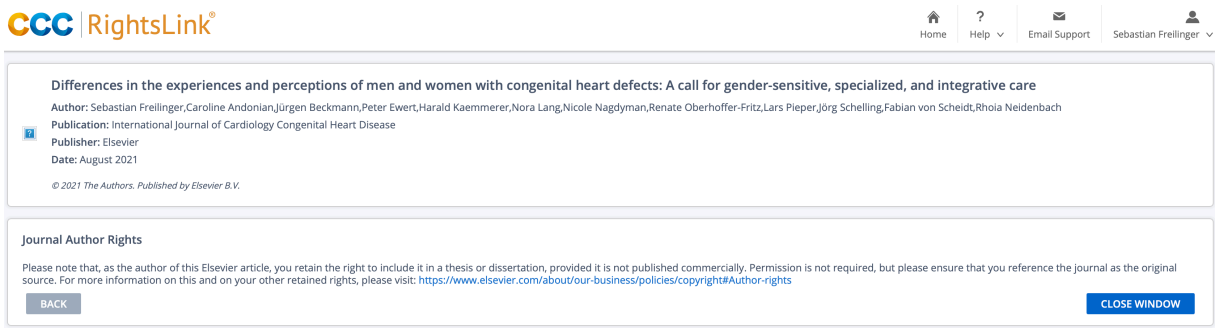

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Differences in the experiences and perceptions of men and women with congenital heart defects: A call for gender-sensitive, specialized, and integrative care

Author: Sebastian Freilinger,Caroline Andonian,Jürgen Beckmann,Peter Ewert,Harald Kaemmerer,Nora Lang,Nicole Nagdyman,Renate Oberhoffer-Fritz,Lars Pieper,Jörg Schelling,Fabian von Scheidt,Rhoia Neidenbach
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Provision of medical health care for adults with congenital heart disease associated with aortic involvement

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