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ORIGINAL ARTICLE

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Changing prevalence of severe congenital heart disease: Results from the National Register for Congenital Heart Defects in Germany

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Abstract

Objective: To assess the prevalence of congenital heart disease (CHD) in Germany in relation to phenotypes, severity and gender.

Design: Cross-sectional registry study.

Setting: We analyzed data from patients with CHD born between 1996 and 2015.

Patients: A total of 26 630 patients, registered with the NRCHD, were born between 1996 and 2015. 10 927 patients were excluded from the current analysis due to prior registration with the NRCHD under the German PAN Prevalence Study, which showed a potential bias in the inclusion of this patient population (proportion of mild cardiac lesions was comparatively high due to improved diagnostic capability for earlier identifying minor lesions). At least 15 703 patients with demographic data and detailed medical information were included in the current study.

Interventions: None.

Outcome Measures: Prevalence of CHD in Germany differentiated into gender, severity, and phenotype.

Results: In total, 15 703 patients with CHD (47.1% female) were included in this study. The five most common phenotypes were found to be ventricular septal defect (19.2%), atrial septal defect (13.0%), Tetralogy of Fallot (9.3%), univentricular heart (9.4%), and coractation of the aortae (7.0%). The prevalence of CHD in regard to severity changed over the duration of the observation period. From 1996 to 2007, the number of simple CHD rose steadily ($P < .001$), whereas the number of severe CHD has grown significantly since 2008/2009 ($P < .001$). In regard to gender, the prevalence of simple CHD was higher in females, whereas complex lesions were more common in males ($P < .001$).

Conclusions: Our study shows a growing number of registered severe CHD in the recent decade in Germany. This development is noteworthy as it implicates a growing demand for first intensive hospital care, expert pediatric cardiologic aftercare, and consequently higher economic impact for this patient population.

KEYWORDS
congenital heart disease, prenatal diagnostic, prevalence

1 | INTRODUCTION

Congenital heart disease (CHD) is the most common type of congenital single organ malformation, significantly contributing to infant mortality and morbidity.[1,2] Several studies have shown a temporal variation in both the overall prevalence and prevalence of specific CHD phenotypes.[3–6] Though, these studies reported conflicting results due to differences in setting, study design, examined cohorts, and disease classification. An important meta-analysis by Hoffmann and Kaplan on the incidence of CHD detected that some studies were biased by an inadequate detection rate, for instance by omitting mild cases when the recruitment site is a specialized clinic. Other studies may include all cases, but often are restricted to small, local restricted cohorts included with the consequence that results cannot be translated to the larger population.[1] Marelli et al. published the huge empirical data of CHD prevalence by analyzing data from the Canadian healthcare system, reporting 11.89 cases of CHD per 1000 children, 4.09 per 1000 adults, and 5.78 per 1000 in the general population.[7] In Germany, Lindinger et al. provided essential knowledge with their area wide survey of CHD ("PAN" Prevalence Study). The study included live births diagnosed with a CHD within the first year of life between July 2006 and June 2007, in Germany. 7245 children with CHD were reported by 260 pediatric cardiology institutions resulting in an overall CHD prevalence of 1.08%.[8] Helm et al. compared the prevalence rates of the PAN study and the National Register for Congenital Heart Defects (NRCHD) and reported that the NRCHD is a clinical registry with primarily clinical healthcare relevant cases.[9] It must be pointed out that all CHD were included in the PAN study regardless of their actual clinical relevance. Therefore, the proportion of mild cardiac lesions was comparatively high in the examined time frame, due to an improved diagnostic capacity for earlier identification of minor lesions.

Improvements in prenatal diagnostic and therapy especially of severe CHD are known to influence the prevalence of CHD. Fetal echocardiography can detect CHD at very early stages of gestation and allows parents to carefully consider pregnancy termination.[10–12] Today, rising demand for genetic analysis and prenatal screenings, such as for Down syndrome, which is often associated with the occurrence CHD, contributes to a higher termination rate of pregnancies with severe CHD.[6] Conversely, professional counseling from specialists led to improvements in therapy of severe CHD in the last years with higher survival rates of, for example, functional univentricular hearts.[13] Due to the differing international results in the prevalence of CHD presented above and the rising influence of prenatal CHD diagnosis, we aimed to assess the current prevalence of clinically relevant CHD in Germany.

2 | METHODS

2.1 | Study design and setting

Objective of this study was to assess the prevalence of CHD in Germany in relation to phenotypes, severity and gender. Prevalence is defined as the number of affected persons (in this case: CHD) present at any time.[1] All data were derived from the NRCHD database in Germany. All CHD patients, who were born between 1996 and 2015, with available detailed medical data, were enrolled in the current study, except for those who were previously registered in the PAN Study. This population was omitted due to a comparatively high proportion of minor cardiac lesions diagnosed at earlier stages of life. NRCHD registration is facilitated by collaboration between treating institutions and self-help groups, thereby including only patients with clinically apparent CHD requiring hospital treatment. Thus, the prevalence rate recorded in the NRCHD for particular cases can differ from those established by studies with data from birth-cohort screenings.[9] Moreover, due to a lengthy registration and data storage process, the number of registered CHD patients, born in 2016/2017, was too small for a representative analysis and, therefore, not included in our study.

2.2 | National Register for Congenital Heart Defects

The NRCHD is the national repository for medical data on patients with CHD in Germany. Consisting of 52 582 members (as of May 2017), the NRCHD is Europe's largest registry of CHD patients providing a considerable cohort for representative studies.[9] Registration is voluntary through self-enrollment of patients affected by CHD or their parents, which is facilitated through collaborations between all treating institutions and self-help groups. The NRCHD has extensive experience in data collection via online surveys. The established data infrastructure of the NRCHD allows data to be stored within the framework of a specific data protection concept, which is registered with the Berlin Official for Data Protection and Freedom of Information (Nr. 531.390). General approval by the ethical review board of the Charité University Hospital Berlin is available for all research conducted within the scope of the NRCHD.

2.3 | Statistical analysis

The cardiac diagnoses were arranged in accordance with classification of the International Paediatric and Congenital Cardiac Code (IPCC code).[14] For our analysis, diagnoses were classified according to the severity of CHD.[15] The CHD diagnoses were assigned to four groups: simple CHD, moderate CHD, complex CHD and others (Table 1). The statistical analyzes are descriptive. The chi-square test was used for group comparisons including nominal data. Alpha error adjustment in multiple comparisons was not performed due to the study's conception being explorative and descriptive and since we wanted to avoid overlooking potential influencing factors.[16] SPSS (version 22) was used for statistical analyses.[17]

3 | RESULTS

In total, 15 703 patients with CHD (47.1% female) were included in the statistical analyzes. The overall distribution of CHD phenotypes is shown in Table 2, including the five most common phenotypes:

TABLE 1 Classification of CHD[15]

Simple CHD
Atrial septal defect
Persisting foramen ovale
Pulmonary valve stenosis
Ventricular septal defect
Others
Moderate CHD
Aortic valve disease
Coarctation of the aorta
Ebstein's anomaly
Partial anomalous pulmonary venous drainage;
Tetralogy of Fallot
Others
Complex CHD
Atrioventricular septal defect
Congenitally corrected transposition of the great arteries
Coronary artery anomaly
Interrupted aortic arch
Total anomalous pulmonary venous drainage
Transposition of the great arteries
Tricuspid atresia
Univentricular heart
Others
Nonclassified
Cardiomyopathy
Marfan syndrome

ventricular septal defect (19.2%), atrial septal defect (13.0%), tetralogy of Fallot (9.3%), univentricular heart (9.4%), and cortication of the aortae (7.0%).

3.1 | Prevalence of CHD with respect to CHD complexity

The changing prevalence of CHD regarding the CHD complexity is shown in Figure 1. The number of simple CHD has been steadily rising since 1996, whereas the number of complex CHD has been growing significantly since 2008–2009 ($P < .001$). The rate of moderate CHD was altogether constant over the whole observation period.

3.2 | Gender aspect

Overall, CHD was slightly more often represented in males than females. In those with simple CHD, the prevalence was significantly higher in females, whereas moderate and complex lesions where more common in males ($P < .001$) (Figures 2 and 3). Investigating the relation between gender and CHD complexity over time, there were significant differences on the level $P < .001$ until 2009 and on the level of $P < .01$, until 2011. No significant differences were found in the period of 2012/2013 ($P = .098$) between males and females regarding CHD complexity. In the period of 2014/2015, a significant difference ($P < .05$) between males and females was found.

4 | DISCUSSION

Studies examining the prevalence of CHD vary due to study conception and setting. Furthermore, new developments in therapy management of complex CHD continue to influence the population size of patients with CHD. This is a very important pecuniary aspect for the health care system and insurances due to higher therapy costs of severe CHD. Second, these recent developments are important for

TABLE 2 Overall distributions of CHD phenotypes

	Total sample (n = 15,703)	Male patients (n = 8,301)	Female patients (n = 7,402)
AoV (n = 1,030)	6.6%	8.9%	3.9%
ASD (n = 2,036)	13.0%	9.3%	17.1%
AVSD (n = 858)	5.5%	4.8%	6.2%
ccTGA (n = 135)	0.9%	0.9%	0.8%
CMP (n = 386)	2.5%	2.4%	2.5%
CoroA (n = 91)	0.6%	0.5%	0.6%
CoA (n = 1100)	7.0%	8.2%	5.6%
Ebstein (n = 103)	0.7%	0.5%	0.8%
IAA (n = 93)	0.6%	0.6%	0.6%
Marfan (n = 37)	0.2%	0.2%	0.2%
PAA (n = 161)	1.0%	0.9%	1.1%
PAPVD (n = 114)	0.7%	0.7%	0.8%
PaV (n = 701)	4.5%	4.4%	4.6%
PDA (n = 685)	4.4%	3.0%	5.8%
PFO (n = 252)	1.6%	1.4%	1.9%
Shone (n = 23)	0.1%	0.2%	0.1%
Others (n = 803)	5.1%	4.9%	5.3%
TAPVD (n = 116)	0.7%	0.7%	0.8%
TGA (IVS) (n = 706)	4.5%	6.0%	2.8%
TGA (complex) (n = 158)	1.0%	1.1%	0.9%
TOF (n = 1,457)	9.3%	10.1%	8.3%
UVH (n = 1,638)	10.4%	12.1%	8.6%
VSD (n = 3,020)	19.2%	18.0%	20.6%

AoV, aortic valve disease; ASD, atrial septal defect; AVSD, atrioventricular septal defect; ccTGA, congenitally corrected transposition of the great arteries; CMP, cardiomyopathy; CoA, coarctation of the aorta; CoroA, coronary artery anomaly; Ebstein, Ebstein's anomaly; IAA, interrupted aortic arch; Marfan, Marfan syndrome; PAA, pulmonal artery anomaly; PAPVD, partial anomalous pulmonary venous drainage; PaV, pulmonary valve disease; PDA, patent ductus arteriosus; PFO, persisting foramen ovale; Shone, Shone complex; others,; TA, tricuspid atresia; TAPVD, total anomalous pulmonary venous drainage; TGA (IVS), transposition of the great arteries with intact ventricular septum; TGA (complex), transposition of the great arteries; TOF, tetralogy of fallot; UVH, univentricular heart; VSD, ventricular septal defect.
Number in %.

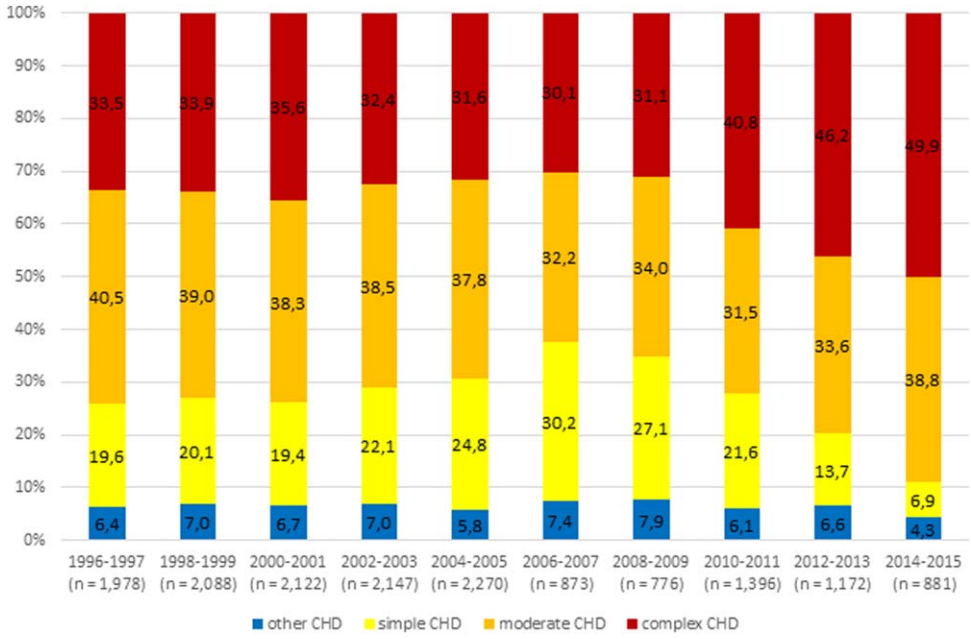

FIGURE 1 Overall changing prevalence (in %) of CHD complexity

prenatal counseling to give parents an all-encompassing informative conversation. Therefore, it is of great interest to research the prevalence of CHD especially regarding severity of CHD.

4.1 | Main results

The prevalence of CHD regarding the CHD complexity has changed substantially over the observation period with a significant growing number of complex defects. Regarding the gender aspect, prevalence of simple CHD was significantly higher in females, whereas complex lesions where more common in males.

4.2 | Comparison with other studies

Various multicenter registry studies worldwide have examined the prevalence of CHD. As study setting is an important influencing factor, we would like to focus for a first comparison on the PAN Prevalence Study in Germany.[5] In their study on frequency and spectrum of CHD in Germany the authors investigated newborns with CHD diagnosed within the first year of life, during the period of July 2006 to June 2007 in Germany. The number of CHD reported by the Departments of Pediatric Cardiology was as follows: 44.9% for mild CHD, 29.9% for moderate CHD, and 25.2% of severe CHD. In line with these results,

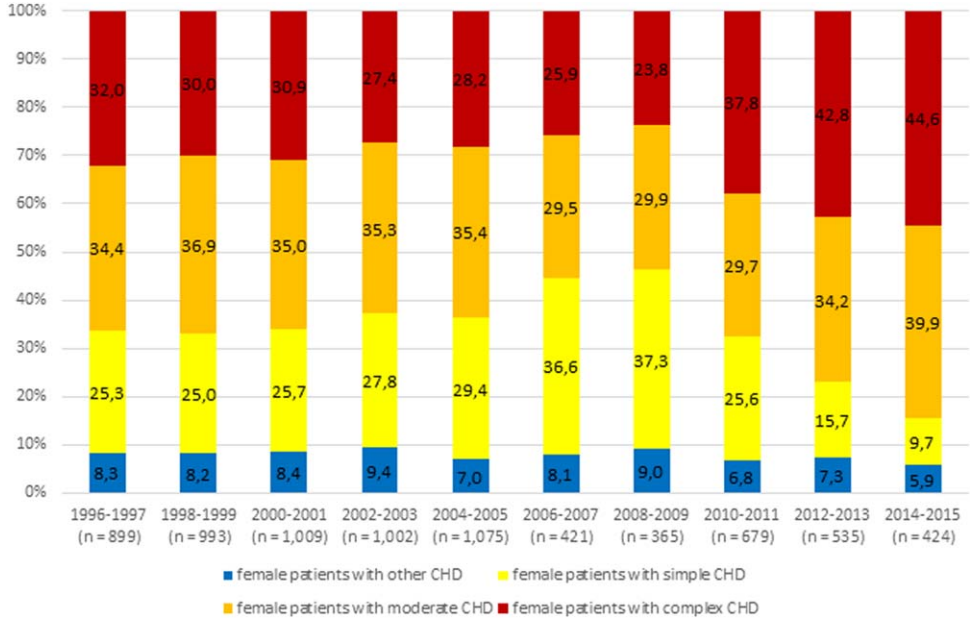

FIGURE 2 Changing prevalence (in %) of CHD complexity in females

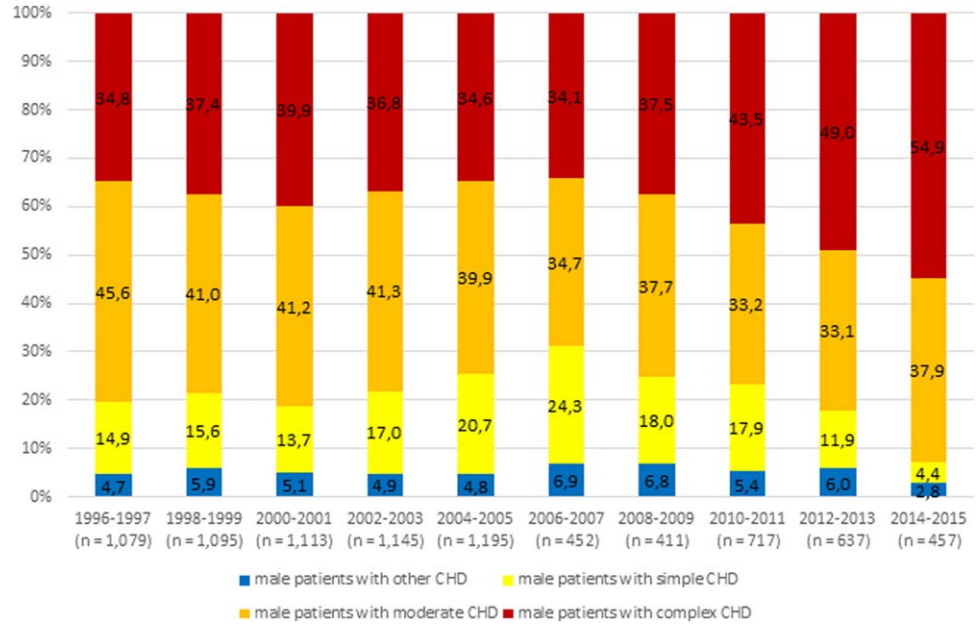

FIGURE 3 Changing prevalence (in %) of CHD complexity in males

we also observed during this period a nearly equal distribution of CHD, though mild CHD was less often represented (30.2 vs 44.9%). This difference can be explained by different study setting, as in the PAN Study newborns were screened for CHD including mild, clinical unapparent CHD. The NRCHD registration is facilitated through collaboration between treating institutions and self-help groups, including patients with clinical apparent CHD requiring hospital treatment. Thus, it can be expected that, in particular cases, the prevalence rates recorded in the NRCHD differ from those established by studies with data of birth-cohort screenings due to different study conceptions.[9] Simple CHD, which can be clinical unapparent, including ventricular septal defects of which 30%-50% can close spontaneously without intervention during the first three years of life, might be underrepresented.[15] This mentioned clinical unobtrusiveness may also explain the lower prevalence of persisting foramen ovale and patent ductus arteriosus, reported in our study. It is known that 90% of isolated patent ductus arteriosus undergo spontaneous closure within the first week of life.[18] Also, persisting foramen ovale can close spontaneously or might be detected later in adulthood as random findings in the follow-up diagnostic due to ischemic stroke.[4,19] None the less, observations proved that the prevalence rates recorded in the NRCHD can be assessed as very accurate.[9] Using medical reports to record diagnostic and outcome data ensure a consistently high level of quality assurance. Second, with more than 50 000 members, a steadily high number of patients across all diagnoses are enrolled in the NRCHD.[9] We could prove that the number of complex CHD is significantly growing since 2008. Studies investigating the prevalence of severe/complex CHD showed various results from a temporal decrease to a constant level of severe/complex CHD.[2,4,10,20–22] Though, it is important to note that the observation period of all these existing and published studies ended before 2008, so recent developments were not considered in these analysis. In addition it has to be noted that due to our study setting, only live births are included, respectively patients with intention or indication to treat. We assume that the increase of severe CHD since 2008 is due to the following various aspects: improved survival outcome due to progress in therapy options, early prenatal diagnosis allowing for all-encompassing informative counseling, and further optimal pre- and perinatal management. Improved surgical outcome was shown by a study to evaluate patients with functionally univentricular hearts in Germany between 2008 and 2015. They showed a 90.4% survival rate on an intention-to-treat basis and a 93.7% survival rate after surgery (Giessen-Hybrid; Norwood procedure).[13] This increasing number of patients with severe CHD with consequently higher therapy costs is noteworthy for the health care policy, systems, and insurances. To give an idea, hospital costs associated with cardiovascular anomalies were about $1.4 billion in the US in 2004.[23] If costs are differentiated to the various CHD phenotypes, this impact becomes more clearly: in our hospital, therapy costs for correction of VSD (without severe postoperative complications) are about 19 000 €, for correction of TOF about 24 000 €. In contrast, hospital costs for the Norwood-I procedure in patients with hypoplastic left heart syndrome amount in case of long ventilation time (what is usually the case) about 110 000 €. In case of severe complication with consecutive long hospitalization and intensive therapy, costs can be even up to 250 000 €.

Examining the gender aspect in our study cohort, we found that overall CHD was slightly more often represented in males. In those with simple CHD, the prevalence was significantly higher in females, whereas complex lesions where more common in males. This is in line with previous studies, showing shunt lesions (ASD, VSD, PDA), in our study cohort defined as simple CHD, to be more often in females.[7] Furthermore, Marelli et al. reported a male predominance in severe/complex defects with transposition of the great arteries and aortic coarctation. Thus, further studies are necessary to determine this gender predominance in certain CHD phenotypes.

4.3 | Limitations

Due to the registration process of the NRCHD, we included only patients with clinical apparent CHD, respectively CHD requiring hospital treatment. This may lead to an underrepresentation of simple, clinical unapparent CHD (ie, ventricle septum defect, persisting foramen ovale, patent ductus arteriosus) and bias the rate of moderate and complex CHD. Furthermore, we do not know what percentage of included patients was preceded by prenatal diagnostic testing, what proportion of affected pregnancies was terminated, or how many parents decided for compassionate care.

This study is a cross-sectional retrospective registry study, therefore, relations of cause and effect cannot be concluded. As previous studies also showed differences due to study setting and location, the results should be generalized to patients beyond Germany only with caution.

5 | CONCLUSION

With approximately 16 000 study participants, we present a large database of CHD prevalence and analysis of recent developments base on an observation period up to 2015. Our study shows an increasing number of complex CHD in recent years. This development is noteworthy, as it points to a growing demand for intensive hospital treatment for these patients and expert pediatric cardiologic aftercare. Furthermore, the pecuniary aspect of this development will impact the health care and insurance systems, due to higher therapy costs of severe CHD. Finally, prenatal counseling should take these recent developments into account to give expecting parents an all-encompassing and informative consultation.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Manuscript writing: Pfitzer
Study conception: Pfitzer, Bauer, Schmitt
Statistical analysis: Pfitzer, Helm, Schmitt
Data assessment: Helm
Manuscript revision: Rosenthal, Ferentzi, Bauer, Berger, Schmitt

ETHICAL APPROVAL

"All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

INFORMED CONSENT

"Informed consent was obtained from all individual participants included in the study."

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