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Original Article

Representativeness of the German National Register for Congenital Heart Defects: a clinically oriented analysis

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Abstract *Background:* Approximately 6000 children are born with CHD in Germany each year. It is increasingly rare that these children die from their chronic illness. In the present study, data recorded in the National Register for Congenital Heart Defects with respect to the prevalence of specific lesions and sex distribution are compared with that recorded in a published German prevalence study (Prevalence Study) and with the meta-analysis by van der Linde et al. *Methods:* A descriptive data analysis was performed using a minimal data set. The demographic data included sex and birth year; the medical data comprised the cardiovascular diagnosis according to the short list of the International Paediatric and Congenital Cardiac Code. *Results:* As the data analysis shows, the National Register is a clinical register including primarily clinical cases/cases relevant to healthcare. The prevalence values and sex ratios recorded in the register are closer to the values given in the literature than those determined by the Prevalence Study. Severe CHD was slightly over-represented in the National Register compared with the van der Linde et al meta-analysis. The deviations with respect to prevalence values are within an acceptable range. *Conclusion:* With its 48,000 patients, the National Register plays a unique and important role for research in the field of CHD. Samples from the National Register can be used as a gold standard for future studies, as the patient population registered in it can be considered representative of CHD in Germany and Europe.

Keywords: CHD; prevalence; clinical register; representative; sex distribution

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Each year, ~6000 children are born with CHD in Germany.[1,2] Owing to improved diagnostic and therapeutic methods, it is increasingly rare that these infants and children die from their chronic heart disease and it is increasingly frequent that they reach adulthood.[3–5]

In the past, doubts have been raised regarding the representativeness and possible bias in the use of data from the German National Register for Congenital Heart Defects. This study investigates these issues in order to better understand the quality of past and future studies that have used data from the National Register. Therefore, in the present study, data recorded in the National Register for Congenital Heart Defects with respect to the prevalence of specific lesions and sex distribution are compared with that recorded in a published German prevalence study – prevalence of CHD in newborns in Germany; study period 2006–2009 – and with the meta-analysis published by van der Linde et al.[2,6]

Registration to the National Register for Congenital Heart Defects is voluntary. Parents giving birth to a child with CHD in Germany are given the opportunity to enrol their child in the National Register. By consenting to this, they have the option of taking part in studies and of regularly receiving

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information on the current state of research in the field of CHD. Registration is promoted by patients' and parents' associations through their websites and in print. There should be no exception to this process, but we do not know whether every physician always offers registration to each family or how many families decline registration to the Register; however, the National Register comprises data from ~48,000 members (as of September, 2014) including children, adolescents, and adults with CHD. This makes it the largest patient database on CHD in Europe.

An area-wide survey of CHD in newborns in Germany (Prevalence Study) was realised in the form of a mandatory nationwide prospective epidemiological study by the German Competence Network for Congenital Heart Defects, which is funded by the Federal Ministry of Education and Research. The project involved hospital departments of paediatric cardiology, children's hospitals, and medical practices for paediatric cardiology. During the course of the Prevalence Study, CHD diagnoses were recorded from a total of 19,462 patients born alive between 1 July, 2006, and 30 June, 2009, to mother's residing in Germany at the date of birth.[2] Until then, comparable data had not been available for Germany.

The meta-analysis by van der Linde et al was based on 114 single studies. It included a total of 24,091,867 live births, of which 164,396 (0.68%) were affected by CHD. Stratification according to sex was not performed.[6]

Both the Prevalence Study and the meta-analysis by van der Linde et al are epidemiological investigations, whereas the National Register represents a clinical register for CHD.[2,6] The goal of optimised, area-wide medical care in line with actual clinical need calls for an exact analysis of currently available data records.

Material and methods

In the present analysis, 2 years of birth recorded in the National Register (2004 and 2005) and two recorded in the Prevalence Study (2007 and 2008) were compared with each other with respect to the prevalence of CHD in newborns and the frequency distribution of specific CHD diagnosis groups. These results were then compared with the disease frequency reported in the meta-analysis by van der Linde et al.[2,6] For this purpose, a minimal data set was used for descriptive analysis.

The demographic data include sex and birth year; the medical data comprise the cardiovascular diagnosis according to the International Paediatric and Congenital Cardiac Code short list, specifically the Association for European Paediatric Cardiology-derived version.[7] As the major proportion of patients included in the Prevalence Study were also enroled in the database of the National Register, years of birth that did not overlap were selected for data analysis to avoid statistical bias.

The inclusion criterion for registration in the National Register and for participation in the Prevalence Study was the presence of CHD. Patients with multiple defects or complex CHD, severe co-morbidities such as chromosomal anomalies, prematurity, etc., are also included. In the case of a premature birth, a patent ductus arteriosus is only counted if it remains patent over 3 weeks past the calculated date of birth.

There were 1893 newborns with CHD recorded in the National Register during 2004 and 2005 (992 male, 901 female).

During 2007 and 2008, a total of 9141 newborns with CHD were recorded by the Prevalence Study survey and were included in the analysis (4315 male, 4826 female).

The patients from the National Register and the Prevalence Study who were included in the analysis had altogether 155 different main cardiac diagnoses. These 155 diagnoses were assigned to eight diagnosis groups according to the classification system used by van der Linde et al. In addition, a ninth diagnosis group (other CHD) was defined, including all congenital heart malformations from the National Register and the Prevalence Study that could not be assigned to one of the groups defined by van der Linde et al. Since other CHD were not labelled as a ninth diagnosis group by van der Linde et al (see Tables 1 and 2) as in the present analysis, the percentages of the eight diagnosis groups defined by van der Linde at al. amount to only 84% of those recorded by the National Register and the Prevalence Study.[2,6] Owing to the variety of individual cardiac diagnoses in the group of other heart defects, this group is not further considered below. This decision was made, on the one hand, because we judged that the small numbers within each diagnostic category were of low significance, and, on the other hand, due to the inability to compare the results with those reported in the meta-analysis.

Therefore, only the assignment of diagnoses to different diagnosis groups as described facilitates valid comparison of the data from the National Register, the Prevalence Study, and the meta-analysis. The defined diagnosis groups are as follows: "ventricular septal defect", "atrial septal defect", "patent ductus arteriosus", "pulmonary stenosis", "tetralogy of Fallot", "coarctation of the aorta", "transposition of the great arteries", "aortic stenosis", and "other CHD". If multiple cardiac diagnoses are present, assignment to one of the diagnosis groups depends on the judged medical significance of the present cardiac diagnoses – for

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Table 1. Prevalence rates of CHD according to the National Register for the years 2004/2005 and according to the meta-analysis by van der Linde et al[6].

	Register (2004)						Register (2005)						
	Frequency			%			Frequency			%			
	m	f	Total	m	f	Total	m	f	Total	m	f	Total	Meta-analysis (n = 164.396 (%))[6]
VSD	134	124	258	25.8	27.0	26.3	107	130	237	22.7	29.5	26.0	34
ASD	51	77	128	9.8	16.7	13.1	54	81	135	11.4	18.4	14.8	13
PDA	14	32	46	2.7	7.0	4.7	17	26	43	3.6	5.9	4.7	10
PS	36	33	69	6.9	7.2	7.0	31	27	58	6.6	6.1	6.4	8
TOF	50	38	88	9.6	8.3	6.9	51	27	78	10.8	6.1	8.5	5
CoA	51	27	78	9.8	5.9	8.0	42	35	77	8.9	7.9	8.4	5
TGA	30	17	47	5.8	3.7	4.8	43	9	52	9.1	2.0	5.7	5
AS	32	14	46	6.2	3.0	4.7	28	11	39	5.9	2.5	4.3	4
Other CHD	122	98	220	23.5	21.3	22.4	99	95	194	21.0	21.5	21.2	
Total	520	460	980	53.1	46.9	100	472	441	913	51.7	48.3	100	

AS = aortic stenosis; ASD = atrial septal defect; CoA = coarctation of the aorta; f = female; m = male; PDA = patent ductus arteriosus; PS = pulmonary stenosis; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect

Table 2. Prevalence rates of CHD in the Prevalence Study for the years 2007/2008 and according to the meta-analysis by van der Linde et al[6].

	Prevalence Study (2007)						Prevalence Study (2008)						
	Frequency			%			Frequency			%			
	m	f	Total	m	f	Total	m	f	Total	m	f	Total	Meta-analysis (%)[6]
VSD	1143	1453	2596	47.5	53.7	50.8	927	1196	2123	48.6	56.4	52.7	34
ASD	328	467	795	13.6	17.3	15.6	230	339	569	12.1	16.0	14.1	13
PDA	119	128	247	4.9	4.7	4.8	89	64	153	4.7	3.0	3.8	10
PS	134	186	320	5.6	6.9	6.3	115	134	249	6.0	6.3	6.2	8
TOF	95	83	178	3.9	3.1	3.5	86	54	140	4.5	2.5	3.5	5
CoA	107	78	185	4.4	2.9	3.6	92	78	170	4.8	3.7	4.2	5
TGA	93	35	128	3.9	1.3	2.5	61	33	94	3.2	1.6	2.3	5
AS	96	30	126	4.0	1.1	2.5	51	24	75	2.7	1.1	1.9	4
Other CHD	292	244	536	12.1	9.0	10.5	257	200	457	13.5	9.4	11.3	
Total	2407	2704	5111	47.1	52.9	100	1908	2122	4030	47.3	52.7	100	

AS = aortic stenosis; ASD = atrial septal defect; CoA = coarctation of the aorta; f = female; m = male; PDA = patent ductus arteriosus; PS = pulmonary stenosis; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect

example, in the presence of an atrial septal defect and a ventricular septal defect in a patient, the decision whether this patient will be assigned to the atrial septal defect or the ventricular septal defect group was achieved by a multi-step quality management system based on medical documents (medical reports, operating reports). A list of all IPCCC codes that went into the nine different diagnosis groups can be found in the appendix of this article.

The statistical analyses are confined to mere descriptive assessment and analysis of the collected data. Each year of birth was classified and broken down to percentages in strict observance of the approach followed by van der Linde et al.[6] Regarding the data recorded by the National Register and the Prevalence Study, gender distribution was also examined.

Results

The meta-analysis carried out by van der Linde et al examined the prevalence rates of CHD regardless of sex. With a prevalence of 34%, ventricular septal defect is stated as the most frequent CHD, followed by atrial septal defect (13%), patent ductus arteriosus (10%), pulmonary stenosis (8%), tetralogy of Fallot, transposition of the great arteries, and coarctation of the aorta (5% each), and aortic stenosis (4%).[6]

The comparison of the 2 years of birth of 2004 and 2005 as recorded by the National Register revealed a deviation of an average of 0.8% between the 2 years (minimum 0.0% to maximum 1.7%) in the defined diagnosis groups. In three of the nine diagnosis groups – that is, atrial septal defect, tetralogy of Fallot, and others – the difference in prevalence between the 2 years was <1.0%. For 2005, the prevalence of aortic stenosis as determined by the National Register was 4.3%. This value deviates from the data of van der Linde et al by only 0.3%, the lowest value. In contrast, the greatest deviation from the results of van der Linde et al was found regarding the diagnosis group ventricular septal defect: the prevalence of 26% as defined by the National Register for 2005 differs from the numbers given by van der Linde et al by 8%.[6] A comprehensive overview of the data is given in Table 1.

The 2 recorded years of birth showed deviations regarding the prevalence of male and female patients within the defined diagnosis groups. Thus, the prevalence rates of male and female patients recorded for the year 2004 differed by an average of 2.8% across all diagnosis groups – for example, the largest deviation was found in the diagnosis group atrial septal defect (6.9%), whereas the diagnosis group pulmonary stenosis showed the smallest deviation of 0.3% (see Table 3). For 2005, the average sex-specific deviation was 3.7%, with the maximum in the transposition of the great arteries group at 7.1% and minimum in the pulmonary stenosis group at 0.5%. For the calculation of sex ratios, the average value for each sex regarding the different diagnosis groups was calculated for each year of birth as recorded in the National Register (2004 and 2005). The calculated values were then compared. Detailed results regarding sex differences in the defined diagnosis groups (ratio male:female) can be found in Table 3.

The years of birth 2007 and 2008 as recorded by the Prevalence Study showed an average deviation of 0.7% (minimum: 0.0%, maximum: 1.9%) between the 2 years with respect to the prevalence rates in the defined diagnosis groups. In two of the nine diagnosis groups – that is, ventricular septal defect and atrial septal defect – the differences in prevalence between the 2 years were <1.0%. Comparing the results of the Prevalence Study with those by van der Linde et al, the lowest deviation of 1.4% was found regarding the prevalence of coarctation of the aorta recorded for 2007 (3.6%). The largest deviation, on the other

Table 3. Sex ratios of CHD according to the National Register for the years 2004/2005 and according to the Prevalence Study for the years 2007/2008.

	Register (2004/2005)			Prevalence Study (2007/2008)		
	m (%)	f (%)	Ratio m:f	m (%)	f (%)	Ratio m:f
VSD	24.3	28.3	1:1.2	48.1	55.1	1:1.2
ASD	10.6	17.6	1:1.7	12.9	16.7	1:1.3
PDA	3.2	6.5	1:2.2	4.8	3.9	1.2:1
PS	6.8	6.7	1:1	5.8	6.6	1:1.1
TOF	10.2	7.2	1.4:1	4.2	2.8	1.5:1
CoA	9.4	6.9	1.5:1	4.6	3.3	1.4:1
TGA	7.5	2.9	2.6:1	3.6	1.5	2.4:1
AS	6.1	2.8	2.2:1	3.5	1.1	3.2:1

AS = aortic stenosis; ASD = atrial septal defect; CoA = coarctation of the aorta; f = female; m = male; PDA = patent ductus arteriosus; PS = pulmonary stenosis; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect

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hand, was found regarding the diagnosis group "ventricular septal defect" as calculated on the basis of the Prevalence Study for the year 2008: the prevalence of 52.7% differs from that of van der Linde et al by 18.7%. A detailed overview of the data is shown in Table 2.

Regarding the year of birth 2007, as recorded by the Prevalence Study, the prevalence rates in male and female patients across all diagnosis groups differed by an average of 2.5%. The largest deviation of 6.2% was found in the diagnosis group "ventricular septal defect", whereas the diagnosis group "patent ductus arteriosus" showed the smallest deviation of 0.2% (see Table 3). For the year 2008, the average sex-specific deviation was 2.7%, with the maximum in the group "ventricular septal defect", 7.8%, and the minimum in the group "pulmonary stenosis", 0.3%.

Discussion

With deviations for the years 2004 and 2005 of between 0.0 and 1.7%, the prevalence rates as recorded in the National Register can be assessed as very accurate. This suggests, on the one hand, a consistently high level of quality assurance regarding the recording of diagnostic data by using medical reports in the National Register; on the other hand, it points to a consistently high number of patients across all diagnoses enrolling in the National Register. Minor prevalence differences can be attributed to medium sample sizes.

Larger differences between the prevalence rates calculated by van der Linde et al on the one hand and the National Register on the other hand, such as those identified for the diagnosis groups "ventricular septal defect" (average deviation of 7.8%) and "patent ductus arteriosus" (average deviation of 5.3%), can be attributed to the nature of the National Register as a clinical register – for example, 30–50% of all ventricular septal defects close spontaneously without intervention during the first 3 years of life.[8] The National Register, however, primarily includes cases that are clinically relevant. Thus, it can be expected that, in particular cases, the prevalence rates recorded in the National Register differ from those established by the meta-analysis of van der Linde et al.[6]

The sex differences with respect to the diagnosis groups seem obvious, and in the case of tetralogy of Fallot they closely match the results given in the literature (ratio male:female): ventricular septal defect (1:1), atrial septal defect (1:2), patent ductus arteriosus (1:2), pulmonary stenosis (1:1), tetralogy of Fallot (1.4:1), coarctation of the aorta (1.7:1), transposition of the great arteries (2:1), and aortic stenosis (3:1).[8] Similar to prevalence deviations regarding the different years of birth, deviations with respect to the sex ratio can be attributed to the sample size. It can be expected that a larger sample size will have the effect of the sex ratios approaching the values given in the literature.

Similarly, ranging between 0.0 and 1.9%, the prevalence differences for the years 2007 and 2008 as recorded by the Prevalence Study can be rated as small. Prevalence deviations can be explained by different sample sizes in the years of birth surveyed and resulting statistical variance. Just as in the National Register, the prevalence rates calculated on the basis of the Prevalence Study differ – although to a much greater extent – from the values given by van der Linde et al with respect to the diagnosis groups "ventricular septal defect" (average deviation of 17.8%) and "patent ductus arteriosus" (average deviation of 5.7%). As the Prevalence Study is a complete survey of all newborns with CHD in Germany, mild CHD can be expected to be over-represented, whereas severe CHD can be anticipated to be under-represented.[2,6] Likewise, the sex differences in the defined diagnosis groups approximate the values given in the literature, just as in the National Register.[8] Larger deviations from the values given in the literature were found only for the diagnosis groups "atrial septal defect" and "patent ductus arteriosus". This might be due to neonatal diagnosis. It is a well-known fact that both atrial septal defect and patent ductus arteriosus often close spontaneously or are not diagnosed until a later time.[8,9] Whether spontaneous closure occurs more frequently in male patients has not yet been sufficiently studied.[9] The difference in sex ratios compared with the results in the literature and the deviations in prevalence compared with the meta-analysis may also be due to the comprehensive recording of diagnoses of a complex and multidimensional disease pattern without quality assurance measures, among other factors.

The differing prevalence rates of the Prevalence Study on the one hand and the National Register on the other hand particularly emphasise the need for a National Register for CHD. The results of the present data analysis demonstrate that the National Register is a clinical register, which primarily comprises clinical – that is, healthcare relevant – cases. Furthermore, the prevalence rates and sex ratios arrived at by the National Register are closer to the values given in the literature than those recorded in the Prevalence Study.[2,8] It is true that, compared with van der Linde et al, the National Register is characterised by a slight over-representation of severe CHD; however, this may be due to the multitude of studies included in the meta-analysis.[6] Similarly, the deviations with respect to prevalence rates are within an acceptable range. Thus, the National Register - with its 48,000 patients - plays a unique and significant role for Germany. Samples

from the National Register can be used as the gold standard for future studies, as – given a sufficiently large sample size – they can be expected to be representative of CHD in both Germany and the rest of Europe.[10]

Limitations

Unfortunately, a comparison of the sex distribution was possible only between the birth cohorts of the Prevalence Study and those of the National Register, and not with the meta-analysis by van der Linde et al. Of course, it should be taken into consideration that both the Prevalence Study and the meta-analysis by van der Linde et al are epidemiological studies, whereas the National Register is a clinical register. In addition, diagnoses that were not allocated to any of the eight defined diagnostic groups were excluded from the analyses performed.

Conclusions

The concern about a lack of quality in random samples of the National Register is unfounded. The number of patients registered of all ages and with all cardiac diagnoses, including co-morbidities and other medical data, is a unique starting point for studies of all kinds. For the study of individual diagnostic groups, randomised double-blind comparative clinical trials or cohort, or genetic studies, the National Register offers high-quality data for researchers from Germany and around the world.

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Conflicts of Interest

None.

Ethical Standards

All persons (or their legal representatives) included in the National Register and the Prevalence Study gave their informed consent before their inclusion into the study. Both the studies were approved by appropriate ethics committees. The same can be assumed regarding the studies surveyed by van der Linde et al. As the paper at hand is a descriptive evaluation of existing data, no procedures or interventions took place. The present analysis is, thus, in accordance with the ethical standards and does not require separate approval by an institutional review body.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S1047951115001547

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