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Birth prevalence of congenital heart defects in Norway 1994-2009—A nationwide study

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Background The reasons for decreasing birth prevalence of congenital heart defects (CHDs) in several European countries and Canada are not fully understood. We present CHD prevalence among live births, stillbirths, and terminated pregnancies in an entire nation over a period of 16 years.

Methods Information on all births in the Medical Birth Registry of Norway, 1994-2009, was updated with information on CHD from the hospitals' Patient Administrative Systems, the National Hospital's clinical database for children with heart disease, and the Cause of Death Registry. Individuals with heart defects were assigned specific cardiac phenotypes.

Results Among 954,413 births, 13,081 received a diagnosis of CHD (137.1 per 10,000 births, 133.2 per 10,000 live births). The prevalence per 10,000 births was as follows: heterotaxia, 1.6; conotruncal defects, 11.6; atrioventricular septal defects, 5.6; anomalous pulmonary venous return, 1.1; left outflow obstructions, 8.7; right outflow obstructions, 5.6; septal defects, 65.5; isolated patent ductus arteriosus, 24.6; and other specified or unspecified CHD, 12.7. Excluding preterm patent ductus arteriosus, the CHD prevalence was 123.4 per 10,000; per year, the prevalence increased with 3.5% (95% CI 2.5-4.4) in 1994-2005 and declined with 9.8% (–16.7 to –2.4) from 2005 onwards. Severe CHD prevalence was 30.7 per 10,000; per-year increase was 2.3% (1.1-3.5) in 1994-2004, and per-year decrease was 3.4% (–6.6 to –0.0) in 2004-2009. Numbers included severe CHD in stillbirths and terminated pregnancies.

Conclusions The birth prevalence of CHD declined from around 2005. Specifically, the prevalence of severe CHD was reduced by 3.4% per year from 2004 through 2009. (Am Heart J 2014;168:956-64.)

Congenital heart defects (CHDs) are the most common birth defects, reported to affect 5 to 10 per 1,000 live births.[1-5] These cardiac anomalies vary from minor lesions without clinical significance to severe conditions requiring extensive health care and with impaired physical capacity and life expectancy. There is substantial variation in the reported CHD prevalence by year of birth and in different populations.[5] Reliable prevalence estimates are important tools in health care planning, as follow-up through adulthood is necessary for many children with CHD and repeated surgical procedures are often required. Because the etiology of CHD is largely unknown, time trends and changing prevalence in different populations might also give clues to differences in risk factors.[6]

During the 1980s and 1990s, the recorded birth prevalence of CHD increased substantially.[3,5,7] Improved diagnostic tools, such as high-quality ultrasound technology, may have led to increased detection of the mild anomalies in this time period. Although the septal defects accounted for the largest proportion of the overall increase in CHD prevalence,[3,7,8] several studies also reported an increased prevalence of severe heart defects.[3,4,6] However, recent studies have reported that the CHD trend is changing. In Quebec, Canada,[6] the prevalence of severe heart defects started to decrease from 1999. The authors suggested a preventive effect of mandatory folic acid fortification of cereal products introduced in Canada in 1998. In Atlanta, GA, however, where folic acid fortification of flour was introduced at the same time as in Canada, the CHD prevalence continued to increase until 2005.[7] Interestingly, in European countries where there has been no mandatory

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food fortification with folic acid,[9] a study based on the European Surveillance of Congenital Anomalies (EUROCAT) registries 1990-2007[4] found a downward trend in heart defect birth prevalence from 2004 onwards. A shift from severe CHD in live births to severe CHD in terminated pregnancies because of increasing availability of prenatal diagnostics[4] could also have contributed to the drop in live birth prevalence of severe heart defects.

Norway's national health registers afford us the opportunity to conduct a nationwide study of prevalence and time trends of CHDs in live births, stillbirths, and terminated pregnancies.

Methods

Data sources

The Norwegian Population Register has since 1965 registered demographic data and vital status on all residents. The unique personal identification number enables linkage of data between national registries and other data sources.

The Medical Birth Registry of Norway (MBRN) was established in 1967 and has since then recorded information on all births (live births and stillbirths from 16th week of gestation, from 1999 also including terminated pregnancies, and from 2002 all births from 12th week of gestation),[10,11] including medical information of the mothers' health before and during pregnancy, the course of delivery, and the health of the newborn child. The MBRN contains information on CHDs diagnosed shortly after birth based on reports from maternity and pediatric wards.

The National Hospital's clinical database for children with heart disease contains information on all children with a heart condition who have been examined by a pediatric cardiologist or have received surgery or intervention at the National Hospital since 1992.[12] The National Hospital conducted about 80% of congenital heart surgeries in Norway before 2004 and virtually all thereafter.[13]

The multipurpose research project Cardiovascular Disease in Norway[14] established in collaboration between the University of Bergen and the Norwegian Knowledge Centre for the Health Services has retrieved information on cardiovascular diseases including CHDs from the electronic Patient Administrative System (PAS) of all somatic hospitals in Norway, 1994-2009.[15] Up to 20 discharge diagnoses for each hospital stay, as well as information about diagnostic and surgical procedures, are included in the database.

The Cause of Death Registry contains information about the underlying cause of death and up to 6 contributing causes of death, as recorded from the death certificate.

Study population

All births in Norway registered in The Medical Birth Registry from 1994 through 2009 were followed until 31 December 2009 for information on CHDs registered in the hospitals' PAS and until 31 December 2010 for the Medical Birth Registry, the National Hospital's clinical database for children with heart disease, and the Cause of Death Registry.

Case ascertainment and classification of CHDs

Information on individuals with CHD was ascertained from 4 data sources: (1) the National Hospital's clinical database for children with heart disease by van Mierop codes 100, 110, 120, 200, 210, 1002 to 7442[16,17] and *International Classification of Diseases 10th Revision* (ICD-10) codes Q20.0 to Q26.9, Q89.3; (2) the PAS by ICD-9 codes 745.0 to 747.4, 759.3 from 1994 through 1998, and ICD-10 codes Q20.0 to Q26.9, Q89.3 from 1999 onwards; (3) the Medical Birth Registry by ICD-8 codes 746.0 to 747.4, 759.0 from 1994 through 1997, and ICD-10 Q20.0 to Q26.9, Q89.3 from 1997 onwards; and (4) the Cause of Death Registry by ICD-9 745.0 to 747.4, 759.3 from 1994 through 1995, and ICD-10 Q20.0 to Q26.9, Q89.3 from 1996 onwards.

According to this procedure, we identified 16,365 children with codes for CHD. Among them, we excluded heart conditions likely to be physiologically normal, such as 1,727 cases with untreated isolated patent ductus arteriosus (PDA) without mention of the diagnosis after 6 weeks postnatal age; 1,061 untreated isolated atrial septal defects (ASDs) without recording of the diagnosis after 6 weeks (likely persistent foramen ovale); 151 isolated valvular pulmonary stenoses (vPS) without the diagnosis after 6 weeks (likely normal high flow in the pulmonary artery), and 344 cases with a combination of these conditions, leaving 13,082 children with CHD for phenotype classification.

Most children with CHD were registered in several data sources: 36.5% in 2 sources, 14.9% in 3 sources, and 1.2% in 4 sources. When assigning fetuses or children with CHD into cardiac phenotypes, diagnosis codes were first selected from the National Hospital's clinical database (48.0% of the children), then the first entry in the PAS (36.1%), with the priority for diagnoses from the university hospitals with facilities for pediatric cardiac surgery and invasive procedures, the Medical Birth Registry (15.2%), and the Cause of Death Registry (0.7%).

Children with CHD codes were classified into cardiac phenotypes as used by Botto et al,[2,18,19] Øyen et al,[2] and recently by Liu et al,[20] listing the diagnoses in order of priority as follows: *heterotaxia* with or without any other heart defect; *conotruncal defect* (d-transposition of the great arteries [TGA] or tetralogy of Fallot [ToF] with or without atrioventricular septal defect [AVSD], double outlet right ventricle [DORV], conoventricular ventricle septum defect [VSD], pulmonary atresia [PA], or valvular pulmonary atresia [vPA] with VSD [regarded as ToF anatomy], truncus arteriosus, interrupted aortic arch [IAA] type B or type C); *AVSD* with or without anomalous

pulmonary venous return (APVR); *APVR* including total or partial APVR; *left ventricle outflow tract obstruction (LVOTO)* (coarctation of aorta [CoA] or aortic valve stenosis [vAS] with or without VSD, hypoplastic left heart syndrome [HLHS]); *right ventricle outflow tract obstruction (RVOTO)* (hypoplastic right heart syndrome [HRHS], tricuspid atresia, Ebstein anomaly, PA or PvA with intact ventricular septum, and vPS with or without septal defects]; *septal defects* (VSD only, ASD only and recorded from postnatal age 6 weeks, VSD and ASD only); *other complex heart defect* (single ventricle, congenital corrected transposition of the great arteries); *PDA* at postnatal age >6 weeks or with surgical correction, in live births with gestational age ≥37 weeks, or with gestational age <37 weeks (preterm PDA); *other specified heart defect* (eg, isolated valvular malformations not classified as LVOTO or RVOTO and venous malformations); and *unspecified heart defect*. To the last category, we added 89 children who had been registered with diagnosis codes for lethal conditions and alive at age 2 years, but without registered heart surgery or invasive procedure, assuming the heart defect was misclassified.

Severe CHD was defined as heterotaxia, conotruncal defect, AVSD, APVR, LVOTO, RVOTO (except valvular pulmonary stenosis), or other complex heart defect. In a subanalysis, VSDs were divided into those corrected with a percutaneous or surgical procedure and those without such procedures.

Information on chromosome aberrations was retrieved using ICD codes (eighth revision 759.3-759.5, ninth revision 758.0-759.9, 10th revision D82.1, Q90.0-Q99.9) and van Mierop codes (8000-8004, 8009-8025, 8072) in all data sources. In addition, we searched for notes indicating chromosomal disorders in text entry fields in the National Hospital's clinical database for children with heart disease, and Down syndrome registered in the Medical Birth Registry of Norway. The CHD children with extracardiac malformations were identified by ICD codes (eighth revision 740.0-745.9, 748.0-756.9, 759.8-759.9, ninth revision 740.0-744.9, 748.0-756.9, 759.0-759.9, 10th revision Q00.0-Q18.9, Q30.0-Q89.9) and van Mierop codes (8041-8053, 8066, 8074-8076, 8079, 8099), in addition to selected congenital malformations registered in MBRN. The categories chromosomal aberrations and extracardiac malformations were not mutually exclusive.

The age at diagnosis was set to 0 day if the cardiac defect was reported from the maternity ward, otherwise, the age at the first hospitalization reporting CHD, or the age at a cardiac procedure.

Statistical analysis

Birth prevalence was reported as number of persons affected with CHD per 10,000 births (live births, stillbirths, and terminated pregnancies) for the entire period 1994-2009. Then, the prevalences of severe defects combined, VSD, ASD, and PDA were calculated by year of birth. Next, we modeled annual CHD prevalence with The National Cancer Institute's Joinpoint Regression Program version 4.0.4[7,21] to estimate annual percent change (APC) with 95% CIs using the best fitting model. And finally, the yearly prevalence of severe defects was stratified on type of birth, that is, live birth (singleton or multiple birth) with isolated severe heart defect, live birth with severe heart defect and extracardiac defect, stillbirth with severe heart defect, and terminated pregnancy with diagnosed severe heart defect. The median age at diagnosis was calculated for the period 1994-2009 for severe CHD, ASD, and VSD. Cumulative percentile curves for diagnosis were calculated at age 1, 7, 30, 180, 365, and 730 days for severe CHD, and VSD, for the period 2004-2008. The data linkage and all calculations were performed with SAS (version 9.3; SAS Institute Inc, Cary, NC).

Results

Among 954,413 births registered in the Medical Birth Registry 1994-2009, we identified 13,081 individuals with one or more CHDs; the overall birth prevalence was 137.1 per 10,000 (Table I). After excluding isolated PDA in preterm births (gestational age <37 weeks), the birth prevalence of CHD was 123.4 per 10,000. Congenital heart defects were more frequent in girls, with birth prevalence of CHD 136.2 per 10,000 (excluding preterm PDA 123.3 per 10,000), compared to 131.1 per 10,000 (excluding preterm PDA 116.6 per 10,000) in boys ($P < .05$). Severe CHD was found in 2,930 births, with an overall prevalence of 30.7 per 10,000 births and 28.3 per 10,000 live births.

The most common cardiac defects were isolated septal defects; the birth prevalence was 65.5 per 10,000 (Table I). Around three-quarters of these were VSDs, with 48.4 per 10,000 births. The prevalence of conotruncal defects was 11.6 per 10,000; the most frequent was TGA, 3.5, and ToF, 2.7 per 10,000. Left ventricular outlet tract obstructions accounted for 8.7 per 10,000, including HLHS, 2.6, vAS, 3.0, CoA, 3.0, and IAA type A, 0.1 per 10,000, and right ventricular outlet tract obstructions 5.6 per 10,000, among these HRHS, 0.9, Ebstein anomaly, 0.7, and vPS, 3.6 per 10,000. The prevalence of AVSD was 5.6, of APVR 1.1, and of heterotaxia 1.6 per 10,000 births. Other complex heart defects were found in 0.2 per 10,000. Isolated PDA had a prevalence of 24.6 per 10,000. In term births, prevalence of isolated PDA was 10.9 per 10,000. Other specified CHD was found in 6.6, and unspecified CHD in 6.1 per 10,000 births.

The live birth prevalence of CHD was 133.2 per 10,000 and excluding preterm PDA 119.4 per 10,000, whereas the prevalence of CHD among stillbirths or pregnancies terminated for medical reasons was more than 3 times as high, with a prevalence of 478.1 per 10,000 (Table I). Specific cardiac phenotypes, such as heterotaxia,

Table I. Prevalence of CHDs in Norway, 1994-2009

Heart defect phenotype	All births n = 954413		Live births n = 943871		Stillbirths/terminated pregnancies n = 10542	
	n	Prevalence*	n	Prevalence†	n	Prevalence‡
Any CHD	13081	137.1	12577	133.2	504	478.1
CHD excl. preterm PDA	11776	123.4	11272	119.4	504	478.1
Heterotaxia	149	1.6	133	1.4	16	15.2
Conotruncal defect	1110	11.6	1040	11.0	70	66.4
TGA	331	3.5	308	3.3	23	21.8
ToF	258	2.7	243	2.6	15	14.2
DORV	79	0.8	66	0.7	13	12.3
Other conotruncal§	442	4.6	423	4.5	19	18.0
AVSD	530	5.6	492	5.2	38	36.0
APVR	107	1.1	107	1.1	0	0.0
LVOTO	830	8.7	722	7.6	108	102.4
HLHS	244	2.6	154	1.6	90	85.4
CoA	288	3.0	273	2.9	15	14.2
Valv. aortic stenosis	290	3.0	287	3.0	3	2.8
IAA A	8	0.1	8	0.1	0	0.0
RVOTO	532	5.6	506	5.4	26	24.7
HRHS	82	0.9	66	0.7	16	15.2
Ebstein	64	0.7	57	0.6	7	6.6
vPS	348	3.6	347	3.7	1	0.9
Other RVOTO‖	38	0.4	36	0.4	2	1.9
Septal defect, isolated	6248	65.5	6113	64.8	135	128.1
ASD	1350	14.1	1342	14.2	8	7.6
VSD	4620	48.4	4506	47.7	114	108.1
VSD + ASD	189	2.0	179	1.9	10	9.5
Unsp. septal defect	89	0.9	86	0.9	3	2.8
Other complex CHD	20	0.2	20	0.2	0	0.0
Isolated PDA¶	2345	24.6	2345	24.8	0	0.0
At term gestation	1040	10.9	1040	11.0	0	0.0
Preterm gestation	1305	13.7	1305	13.8	0	0.0
Other specified CHD	632	6.6	597	6.3	35	33.2
Unspecified CHD	578	6.1	502	5.3	76	72.1
Associations:						
Conotruncal + AVSD	16	0.2	15	0.2	1	0.9
Septal + LVOTO	79	0.8	78	0.8	1	0.9
Septal + RVOTO	99	1.0	99	1.0	0	0.0

* Prevalence per 10,000 births (live births, stillbirths, terminated pregnancies) registered in the Medical Birth Registry.
† Prevalence per 10,000 live births.
‡ Prevalence per 10,000 stillbirths and terminated pregnancies.
§ Truncus arteriosus, conotruncal VSD, aortopulmonary window, IAA type B or C.
‖ Valvular pulmonary atresia, arterial pulmonary atresia.
¶ PDA recorded after 6 weeks of age or surgically treated.

conotruncal defects, AVSD, and HLHS, showed very high prevalence in stillbirths/terminated pregnancies.

In Table II, the distribution of cardiac phenotypes was shown for multiple birth pregnancies, in children with a chromosomal aberration, and in children with extracardiac birth defects. Among all births with CHD, 8.6% was part of a multiple-birth pregnancy, 10.6% had been diagnosed with a chromosomal aberration, and 21.0% had extracardiac defects. For example, chromosomal aberrations were frequent with AVSD, and extracardiac defects with heterotaxia and conotruncal defects.

In Figure 1, the prevalences of severe CHD, ASD, VSD, PDA, and the remaining defects (vPS, other specified CHD, and unspecified CHD) were presented by year of birth. From 1994 until the beginning of the 2000s, all defects increased in prevalence. Ventricular septal defects had the most marked increase, with roughly doubled prevalence from 1994 to 2007. The prevalence of repaired VSD was stable with a mean prevalence of 5.5 per 10,000 throughout the entire study period 1994-2009 (not shown in figure). Median age at diagnosis for ASD was 323 days; whereas for VSD, PDA, and severe CHD, it was 0 days, that is, diagnosed before leaving the maternity ward. The VSD diagnosis was registered before age 30 days in 92% of the cases, before 6 months in 97%, and within the first year of life in 98% of the VSDs. For severe defects, the

Table II. Multiple birth and extracardiac defects in children with CHD, Norway 1994-2009*

Heart defect phenotype	All births	Multiple birth		Chromosomal aberrations		Extracardiac malformations	
	n	n	(%)	n	(%)	n	(%)
Any CHD	13081	1123	(8.6)	1389	(10.6)	2746	(21.0)
CHD excl. preterm PDA	11776	688	(5.8)	1365	(11.6)	2487	(21.1)
Heterotaxia	149	7	(4.7)	17	(11.4)	135	(90.6)
Conotruncal defect	1110	45	(4.1)	172	(15.5)	349	(31.4)
TGA	331	4	(1.2)	21	(6.3)	66	(19.9)
ToF	258	15	(5.8)	50	(19.4)	89	(34.5)
DORV	79	2	(2.5)	12	(15.2)	38	(48.1)
Other conotruncal†	442	24	(5.4)	89	(20.1)	156	(35.3)
AVSD	530	23	(4.3)	299	(56.4)	134	(25.3)
APVR	107	4	(3.7)	7	(6.5)	33	(30.8)
LVOTO	830	50	(6.0)	89	(10.7)	176	(21.2)
HLHS	244	9	(3.7)	18	(7.4)	47	(19.3)
CoA	288	25	(8.7)	42	(14.6)	70	(24.3)
Aortic stenosis	290	16	(5.5)	28	(9.7)	58	(20.0)
IAA A	8	0	(0.0)	1	(12.5)	1	(12.5)
RVOTO	532	31	(5.8)	35	(6.6)	125	(23.5)
HRHS	82	4	(4.9)	6	(7.3)	26	(31.7)
Ebstein	64	0	(0.0)	3	(4.7)	9	(14.1)
vPS	348	25	(7.2)	24	(6.9)	82	(23.6)
Other RVOTO‡	38	2	(5.3)	2	(5.3)	8	(21.1)
Septal defect, isolated	6248	390	(6.2)	582	(9.3)	1048	(16.8)
ASD	1350	110	(8.1)	183	(13.6)	326	(24.1)
VSD	4620	264	(5.7)	317	(6.9)	641	(13.9)
VSD + ASD	189	10	(5.3)	77	(40.7)	75	(39.7)
Unsp. septal defect	89	6	(6.7)	5	(5.6)	6	(6.7)
Other complex CHD	20	0	(0.0)	1	(5.0)	6	(30.0)
Isolated PDA§	2345	473	(20.2)	81	(3.5)	471	(20.1)
At term gestation	1040	38	(3.7)	57	(5.5)	212	(20.4)
Preterm gestation	1305	435	(33.3)	24	(1.8)	259	(19.8)
Other specified CHD	632	65	(10.3)	37	(5.9)	128	(20.3)
Unspecified CHD	578	35	(6.1)	69	(11.9)	141	(24.4)
Associations:							
Conotruncal + AVSD	16	0	(0.0)	6	(37.5)	6	(37.5)
Septal + LVOTO	79	8	(10.1)	18	(22.8)	25	(31.6)
Septal + RVOTO	99	5	(5.1)	7	(7.1)	29	(29.3)

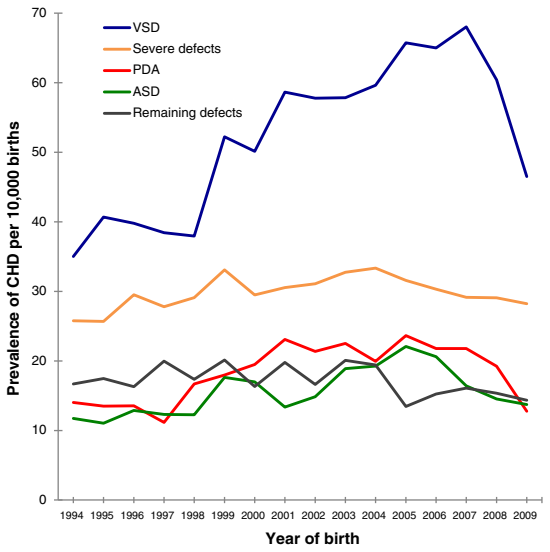
* All live births, stillbirths, and terminated pregnancies registered in the Medical Birth Registry.
† Truncus arteriosus, conotruncal VSD, aortopulmonary window, IAA type B or C.
‡ Valvular pulmonary atresia, arterial pulmonary atresia.
§ PDA recorded after 6 weeks of age or surgically treated.

corresponding cumulative percentages for ages at diagnosis were 85%, 94%, and 95%, respectively.

In Figure 2, we plotted the prevalence of any type CHD (excluding preterm PDA), severe CHD, VSD, and ASD for all births, including stillbirths and terminated pregnancies. Using the Joinpoint Regression Program, the best fit for time trend change was identified. Among all births, the annual increase in total CHD prevalence was 3.5% (95% CI 2.5-4.4) until 2006; thereafter, the prevalence decreased with 9.8% per year (−16.7 to −2.4). Severe CHD prevalence showed an annual increase of 2.3% (1.1-3.5) until 2004 and an annual decrease of 3.4% (−6.6 to 0.0) thereafter. The prevalence of ASD increased with 5.7% (3.2-8.3) per year until 2005 and then decreased with 12.0% (−21.3 to −1.9) per year. Ventricular septal defect prevalence increased with 5.4% (4.0-6.8) per year until 2007 and then showed a marked but nonsignificant annual decrease of 18.6% (−36.7 to 4.6) the last 2 years of follow-up. Among live births only (not shown in the figure), the APC for any type CHD was 3.5% (2.4-4.7) until 2005 and −7.5% (−12.2 to −2.4) thereafter; and for severe CHD, the APC was 1.8% (0.2-3.4) until 2003 and −4.6% (−7.3 to −1.8) thereafter. The time trend curve for severe CHD in live births only did not differ much from the severe CHD time trend in all births.

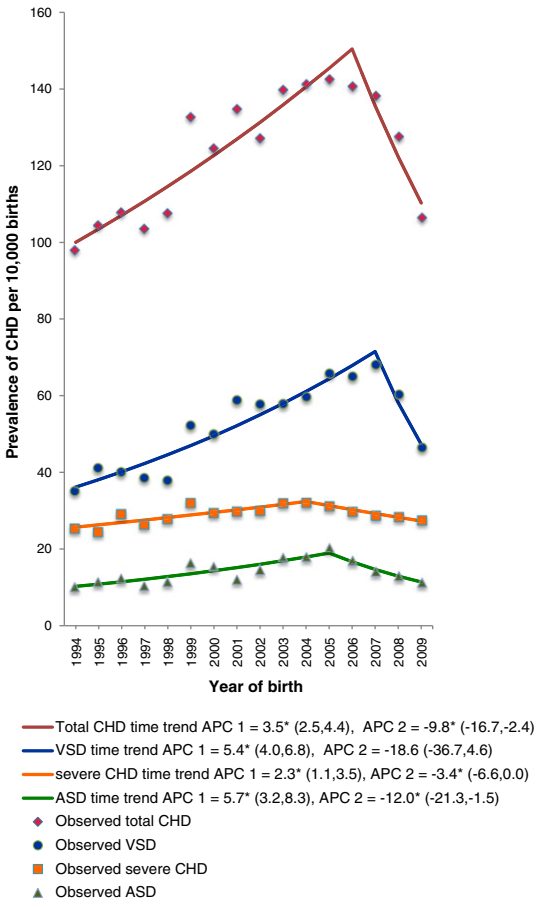
In Figure 3, the annual birth prevalence of severe CHD in Figure 2 was classified into combinations of birth type, plurality (singletons, multiples), and the presence of extracardiac birth defects and/or chromosomal aberrations. The live birth prevalence of singletons with severe

Figure 1



Birth prevalence of CHD per 10,000 live births, stillbirths, and terminated pregnancies by year of birth for isolated VSD, severe defects (heterotaxia, conotruncal defect, AVSD, APVR, LVOTO, RVOTO except valvular pulmonary stenosis, CoA, other complex heart defect), PDA, isolated ASD, and all other remaining defects in 954,413 births, Norway, 1994-2009.

Figure 2



Birth prevalence of CHD per 10,000 live births, stillbirths, and terminated pregnancies by year of birth for all CHD (excluding isolated preterm PDA), VSD, ASD, and severe heart defects (heterotaxia, conotruncal defect, AVSD, APVR, LVOTO, RVOTO except valvular pulmonary stenosis, CoA, other complex heart defect) in 954,413 births, Norway, 1994-2009. Observed and estimated prevalence, and APC with 95% CI, using Joinpoint Regression Program.[21] *$P < .05$.

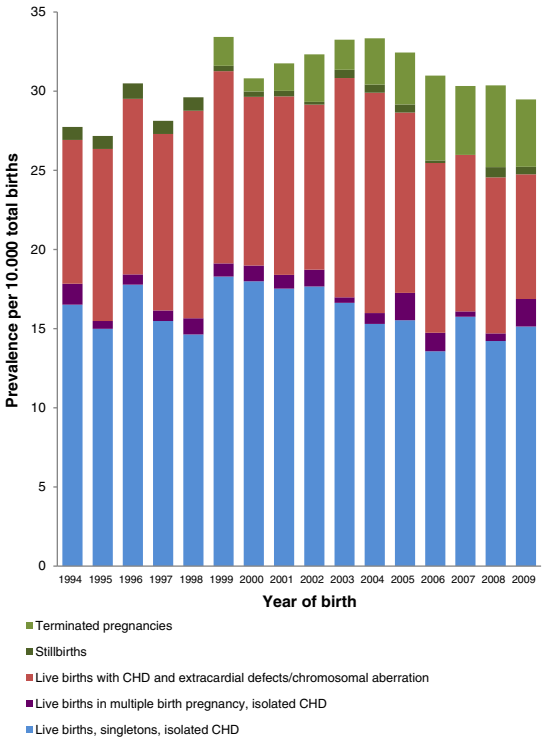
CHD but without extracardiac defects or chromosomal disorders was around 15 per 10,000 births, with a decreasing trend from around 1999 (blue color). Next, the live birth prevalence of twins or triplets with isolated CHD constituted a very small fraction of the total severe CHD prevalence (purple color). The prevalence of live births with severe CHD and extracardiac defects/chromosomal disorders ranged 10 to 14 per 10,000 (red color). Finally, the prevalences for severe CHD in stillbirths and terminated pregnancies increased from 0.9 per 10,000 total births in 1994-1997 to 1.6 in 1998-2001, 3.2 in 2002-2005, and 5.1 in 2006-2009; the overall severe CHD prevalence was 2.7 per 10,000 births (green color). The proportion of terminated pregnancies and stillbirths in births with severe CHD increased from 1994 through 2009; among the total numbers of severe CHD, affected stillbirths and terminated pregnancies combined (n = 257) constituted 8.8%: 3.0% in 1994-1997, 5.0% in 1998-2001, 9.8% in 2002-2005, and 16.9% in 2006-2009 ($P <$ .001).

Discussion

In this nationwide study of CHDs, we identified >13,000 individuals with a CHD among 954,500 live births, stillbirths, and terminated pregnancies registered in the Medical Birth Registry of Norway from 1994 to 2009, yielding a national CHD prevalence of 137.1 per 10,000. There was a significant increase in the prevalence of CHD until 2005, followed by a significant decrease in prevalence, both for total CHD and for severe CHD.

The overall prevalence of CHD in the present study was higher than that reported in similar studies from Denmark, other European countries, and Atlanta, GA.[3,4,7] In the Danish study,[3] the overall prevalence excluding isolated PDA in preterm infants was 103.2 per 10,000 live births versus 123.4 in our study. It is primarily the prevalence of septal defects, particularly VSD, that was higher in the present study, whereas the overall prevalence of severe defects was similar to our findings. The Danish study also reported an increasing prevalence

Figure 3



Birth prevalence of severe CHD by year of birth, stratified on type of birth (live birth, stillbirth/terminated pregnancies, singleton/multiple birth), and type of cardiac defects (isolated or accompanied with extracardiac birth defects and/or chromosomal aberration) in 954,413 births, Norway, 1994-2009. Severe heart defects were heterotaxia, conotruncal defect, AVSD, APVR, LVOTO, RVOTO (except valvular pulmonary stenosis), and other complex heart defects.

of severe heart defects from 1977 to 2005, like the present study. A Canadian study,[6] which included children born in Quebec with selected severe CHDs (ToF, endocardial cushion defects, univentricular hearts, truncus arteriosus, transposition complexes) in the period 1990-2005, reported a prevalence of 15.7 per 10,000 births, which is similar to the prevalence of the corresponding defects in our study and in Denmark. However, the study from EUROCAT, covering 29% of the European birth population, reported considerably lower prevalence of the severe CHD (single ventricle, HLHS, HRHS, Ebstein anomaly, tricuspid atresia, vPA, truncus arteriosus, AVSD, ToF, vAS, TGA, TAPVR, CoA), 17.7 per 10,000,[4] as compared to the present study, 30.7 per 10,000. Although the severe CHD prevalence was lower in the EUROCAT study, the pattern of time trends was similar to the present study with an increase from 1990 to 2004 and a decrease thereafter. The study from Atlanta[7] also reported lower birth prevalence of total CHD and severe CHD, 67.7 and 24.9 per 10,000, respectively, in the period 1978-2005.

As suggested in the previous studies,[3,7,8] the increasing prevalence of minor CHD may be partly explained by improved diagnostic equipment. This applies primarily to the period before year 2000. The continued increase of both minor and severe CHD until 2006, however, has most likely other explanations. We cannot rule out that the CHD prevalence increase could partially be explained by improved reporting of birth defects. In 1999, the Medical Birth Registry implemented a revised notification form, which may have led to higher quality of birth defect reporting, including both mild and severe CHD. Mandatory reporting to MBRN of terminated pregnancies was implemented: from 1999 to 2001 for pregnancies after 16th gestational week and from 2002 after 12th gestational week.[11] This can explain some of the increase in severe CHD from 1994 to 2004.

After the mid-2000s, the prevalence of CHD declined, most markedly for VSD; but also severe defect prevalence declined. The prevalence of CHD could have been underestimated in the last period because of shorter follow-up time. However, VSD demonstrates a distinct murmur usually detected at the maternity ward or the child health clinic, also reflected in our study; 94% of the VSDs had been diagnosed before age 6 months. The large VSD decline the last 2 years of the study period likely represented a true decrease. Most severe defects are symptomatic in early life; in the present study, 94% were diagnosed before 6 months of age. Therefore, the declining prevalence of severe CHD from 2005 through 2009 cannot be fully explained by incomplete case ascertainment due to a shorter follow-up of births in the late period. We acknowledge that ASD, with a median age at diagnosis of 323 days, could have been underestimated in the last period.[3]

At present, the reasons for the decline of CHD prevalence in Norway from the mid-2000-ies are unknown. One explanation for the recent decrease in CHD prevalence in Norway, as in other European countries and Canada, could be an increased intake of folic acid in fertile women. In 1998, food fortification of folic acid was introduced in both Canada and Atlanta, GA, whereas in the European countries, including Norway, official authorities only recommended intake of folic acid supplements for women planning a pregnancy and early in pregnancy.[22] Prenatal vitamin supplementation policy in our study population has been unchanged since 1999. However, the uptake of the recommendations, reflected by an increasing use of preconception folic acid supplementation in Norway, from 5% to 26% in the period 1999-2007,[23] could explain the temporal decrease in CHD prevalence reported in our study, assuming a causal association between folic acid intake and CHD.[24] In Canada, the decreasing prevalence of severe CHD from 1999 coincided with the implementation of food fortification of folic acid. Interestingly, the severe CHD reduction was delayed in Europe starting from the mid-

2000s, which could be explained by a gradual increase of intake of supplements containing folic acid among women in Europe from the end of the 1990s.[4,22] However, in Atlanta, GA, the severe defect prevalence continued to increase until 2005[7] despite the mandatory folate fortification of staple food beginning in 1998.

Alternative explanations for the recent decreasing prevalence of severe CHD in Canada and Europe could be other preventive factors, for example, cessation of maternal smoking,[25] or better monitoring of women with diabetes[26] or other chronic diseases, or maybe a reduction in consanguineous marriages,[27] which are known to be associated with increased birth defect risk. However, in the present study, the births among first-generation immigrants with a high proportion of first-cousin marriage[28] amounted only to 1.1% of all births, with an overall CHD prevalence of 165.8 per 10,000 births. Therefore, a change in consanguineous marriages cannot explain the declining prevalence of CHD in Norway. Finally, we cannot rule out the possibility of random fluctuation; surveillance of CHD remains important in the future.

A limitation of the present study was a possible misclassification of diagnosis codes for CHD because reviewing the medical records for 13,000 patients was not feasible. Besides, we were not allowed by the Ethics Committee to investigate individual medical records. However, almost half of the cases and nearly all the severe defect cases were retrieved from the National Hospital's clinical database for children with heart disease (NHCD). Senior pediatric cardiologists have regularly entered and updated codes for heart defect diagnoses and procedures into this clinical database, which has minimized the possibility of misclassification of severe defects. Furthermore, in the PAS, we selected diagnosis codes from the university hospitals with facilities for pediatric cardiology surgery and invasive procedures. Finally, we cross-checked diagnosis codes in all 2,999 individuals notified with lethal conditions against their survival status at age 2 years and surgery or procedure codes, and identified only 89 (2.8%) misclassified severe defect cases, which we placed in the unspecified CHD category. Congenital heart defects with chromosomal aberrations and/or extra-cardiac defects could have been missed if the cardiac defect was not coded, for example, in stillbirths or terminated pregnancies. However, the proportions of chromosomal aberrations (10.6%) and extracardiac defects (21.0%) were comparable to findings from Denmark (7.0% and 22.3%).[3] There was a risk of including physiological heart conditions notified shortly after birth. To avoid this, untreated ASD, PDA, and vPS only recorded the first 6 postnatal weeks were excluded. Some minor CHDs could have been missed because outpatient clinics' data were only included from the National Hospital's clinical database for children with heart disease. Considering the high prevalence of minor heart defects in the present study, as compared with previous studies, we consider the possible missing outpatient minor defects of little importance.

The strength of the present study was the virtually complete registration of both severe and minor CHD, including cardiac defects in terminated pregnancies, ascertained through 4 national health and administrative registers. This is possible due to the unique personal identification number given shortly after birth, allowing follow-up through life. Because medical care for children is free in Norway and health care is highly developed, nearly all children with CHD are diagnosed at an early age. Finally, the hierarchical structure of our classification system assigning individuals with multiple heart defects to only one cardiac phenotype precluded counting these individuals several times, thus avoiding an overestimation of the total prevalence.

In conclusion, in the present population-based study, we found increasing prevalence of severe CHD from 1994 until 2005 and decreasing prevalence thereafter, corresponding to findings in European and Canadian studies. Although there was an increasing practice of pregnancy termination of fetuses with severe CHD, this contributed little to the time trends in CHD prevalence in Norway. The reasons for the downward change in time trends of CHD and severe CHD from the mid-2000s are unknown but seem related to factors not only changing in Norway. Suggested changes in maternal risk factors, such as an increasing use of folic acid supplementation, or better follow-up of pregnant women with chronic diseases like diabetes has been proposed. Further investigation is required to determine the effect of possible risk factors, as this can provide a basis for treatment, lifestyle advice, or public health interventions.

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Disclosures

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

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