



Severe Congenital Heart Defects and Cerebral Palsy

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Objective To report the prevalence of cerebral palsy (CP) in children with severe congenital heart defects (sCHD) and the outcome/severity of the CP.

Methods Population-based, data linkage study between CP and congenital anomaly registers in Europe and Australia. The EUROCAT definition of severe CHD (sCHD) was used. Linked data from 4 regions in Europe and 2 in Australia were included. All children born in the regions from 1991 through 2009 diagnosed with CP and/or sCHD were included. Linkage was completed locally. Deidentified linked data were pooled for analyses.

Results The study sample included 4989 children with CP and 3684 children with sCHD. The total number of live-births in the population was 1 734 612. The prevalence of CP was 2.9 per 1000 births (95% CI, 2.8-3.0) and the prevalence of sCHD was 2.1 per 1000 births (95% CI, 2.1-2.2). Of children with sCHD, 1.5% (n = 57) had a diagnosis of CP, of which 35 (61%) children had prenatally or perinatally acquired CP (resulting from a brain injury at ≤ 28 days of life) and 22 (39%) children had a postneonatal cause (a brain injury between 28 days and 2 years). Children with CP and sCHD more often had unilateral spastic CP and more intellectual impairments than children with CP without congenital anomalies.

Conclusions In high-income countries, the proportion of children with CP is much higher in children with sCHD than in the background population. The severity of disease in children with CP and sCHD is milder compared with children with CP without congenital anomalies. (*J Pediatr* 2023;262:113617).

Registry-based studies have shown that congenital anomalies occur more frequently in children with cerebral palsy (CP) than in the general population.¹⁻³ Our recent international data linkage study, the largest of its kind to date, found that 22.8% of children with prenatally and perinatally acquired CP had a congenital anomaly and 25.6% of children with postneonally acquired CP had a congenital anomaly.^{4,5} The most frequent non-cerebral congenital anomalies among children with CP were congenital heart defects (CHD). In the population of children with congenital anomalies, CHD is also the most frequent group with up to one-third of all children with congenital anomalies having CHD.⁶ The prevalence of CHD in liveborn children is reported to be 7.2-7.5 per 1000 births, and the prevalence of nonchromosomal severe CHD (sCHD) is reported to be 2.0 per 1000 births.^{7,8} No previous population-based study has been able to determine the prevalence of CP for children born with CHD or specific types of CHD. The insult that leads to CP in children with CHD may be associated with the same prenatal factors or insult that resulted in the congenital anomaly, be associated with the same genetic origin as the anomaly, be associated with abnormal fetal or postnatal circulation, or be postnatally acquired in relation to the cardiac surgery and procedures required.^{3,9-13} This information is important to know in relation to the prevention and treatment of both CP and CHD and for counselling parents.

The aim of this study is to report the prevalence of CP in children with sCHD, the timing of the brain injury (prenatal/perinatal or postneonatal CP) and outcome and severity of the CP.

CHD	Congenital heart defect
CP	Cerebral palsy
EUROCAT	European Network for Surveillance of Congenital Anomalies
GMFCS	Gross Motor Function Classification System
sCHD	Severe congenital heart defect

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Methods

This study of CP and sCHD is phase II of our population-based multicenter data linkage study, the Comprehensive CA-CP Study. It is an international collaboration between CP register networks (Surveillance of Cerebral Palsy in Europe and the Australian Cerebral Palsy Register) and congenital anomaly networks in high-income countries of Europe (European Network for Surveillance of Congenital Anomalies [EUROCAT]) and in Australia. Data were linked between the CP and congenital anomaly register in nine regions of Europe and Australia. Deidentified data were sent to the central site (Cerebral Palsy Alliance, The University of Sydney) and pooled, creating the Comprehensive CA-CP Study dataset. Detailed information regarding the data linkage processes is available.^{4,5,14}

For phase II, we included the 6 regions that were also able to provide denominator data for children with sCHD (without CP): Croatia, Denmark, Norway, Portugal, South Australia, and Western Australia (Figure 1).

All children with CP registered in a participating CP register, born between 1991 and 2009, to mothers residing in the 6 participating regions (Figure 1) were included. Registers required that the diagnosis of CP was verified at age 4 or 5 years, or if death occurred before the age of 5 years, a description of CP after the age of 2 years was required to be included. Children with CP with and without congenital anomalies were included. All live births with a confirmed diagnosis of a sCHD (as defined by EUROCAT¹⁵), but without CP, born during equivalent birth years within each region were also included in the study.

Variables were coded according to the published study protocol, which followed coding guidelines from the Surveillance of Cerebral Palsy in Europe, EUROCAT and Australian Cerebral Palsy Register when possible.¹⁴ To pool data between regions, quality assurance processes were performed

as described in the study protocol. The quality checks were conducted by each participating register before data provision, as well as centrally, and sought to minimize variability between regions.¹⁴

Children with CP were dichotomized by the timing of brain injury, into those with a known postneonatal cause of CP (brain injury after 28 days of life up to age 2 years), and those without a known postneonatal cause, hereafter described as prenatal/perinatal. Clinical data for children with CP were provided by each CP register, where clinical information was verified and confirmed at the age of 4-5 years. The predominant motor CP subtype was coded as spastic bilateral, spastic unilateral, spastic (topography unknown), dyskinetic, ataxic, or unknown/other (including mixed or hypotonia). The Gross Motor Function Classification System (GMFCS) was used to report gross motor function, categorized to match available data.¹⁶ Children were described as primarily walking independently without aides (levels I-II), walking using a mobility aide (III), or using a manual or power wheelchair (IV-V). Intellectual impairment was classified as no impairment (IQ \geq 70), some (mild impairment or IQ 50-69), or moderate to profound impairment (IQ < 50). Vision, hearing and speech were classified as no, some, or severe impairment.¹⁴

Congenital anomaly data were provided for all children (with or without CP) from each congenital anomaly or CP register. Congenital anomaly data were provided by codes from the *International Classification of Diseases*, 9th or 10th revisions, with British Paediatric Association or Australian Modification extension, and written text descriptions. Australian Modification extensions were recoded into British Paediatric Association extensions at the central site. To standardize inclusion and exclusion of congenital anomalies across all participating regions, only major congenital anomalies were included, as defined by EUROCAT.¹⁷ Congenital anomaly data were then recoded into the EUROCAT binary

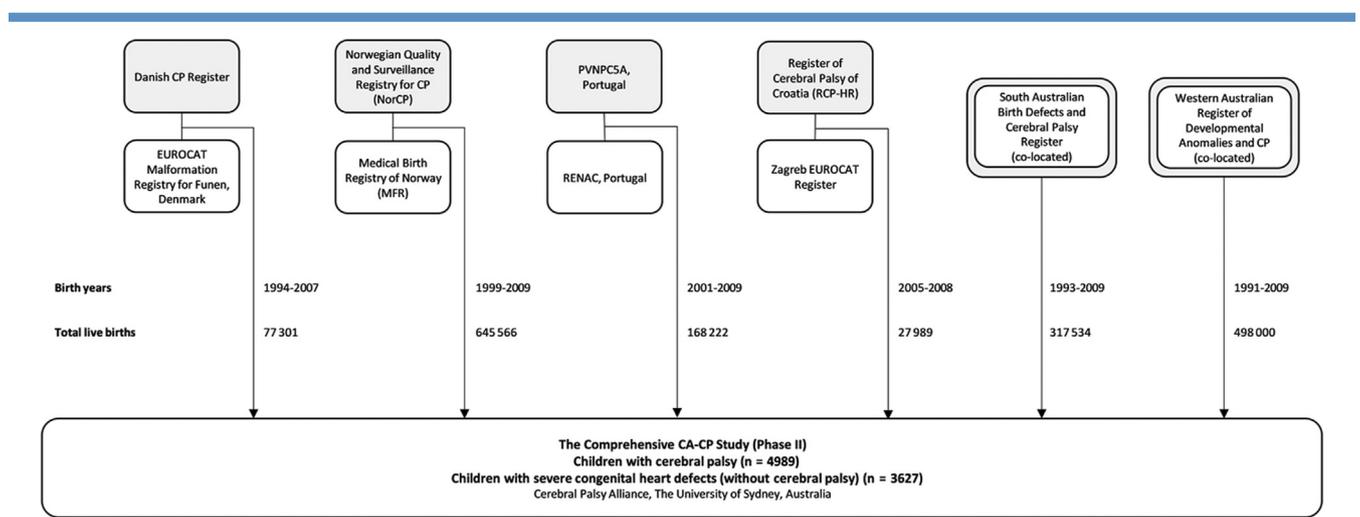


Figure 1. Registers contributing to the study.

(yes, no) subgroup variables, indicating the presence or absence of 114 specific anomalies or groups of anomalies. The focus of this study was sCHD. The EUROCAT definition of sCHD was used, which includes single ventricle, hypoplastic left heart, hypoplastic right heart, Ebstein anomaly, tricuspid atresia, pulmonary valve atresia, common arterial truncus, atrioventricular septal defects, aortic valve atresia or stenosis, transposition of great vessels, tetralogy of Fallot, total anomalous pulmonary venous return, and coarctation of aorta. Children with CP were classified into 4 groups: those with sCHD, nonsevere CHD, only noncardiac anomalies, and no congenital anomalies. Children with sCHD were further classified via EUROCAT software and manual review into isolated cardiac defects, monogenic or chromosomal syndrome, and those with sCHD and associated noncardiac major anomalies.¹⁸

The number of children with sCHD (without CP), CP (without any major congenital anomaly), CP (with sCHD), CP (with nonsevere CHD), and CP (with major noncardiac anomalies) was reported. Prevalence per 1000 live births and 95% CIs were calculated. Descriptive statistics were used to stratify children within each group by sex, birth plurality, gestational age (weeks) and birthweight (grams). The Intergrowth-21st International Newborn Size at Birth Standards application was used for singletons to describe being small for gestational age (reported as <10th centile) and very small for gestational age (<3rd centile) based on sex, gestational age at delivery (completed weeks), and birthweight.¹⁹ The total number of children with sCHD was described, as well as by classification (isolated cardiac defects, monogenic and chromosomal syndromes, and associated noncardiac major anomalies). Clinical outcomes for children with CP were reported descriptively, stratified by the presence of sCHD or no major congenital anomalies. Only the percentages of known data were reported; missing data were reported separately. Proportions were compared between groups of children using the χ^2 test or Fisher's exact

test when $\geq 20\%$ of cell sizes were < 5 . A threshold P value of $< .05$ was set for statistical significance. IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY) and Stata Statistical Software Release 15 (StataCorp LLC, College Station, TX) were used for analysis.

The overarching Comprehensive CA-CP Study has ethical approval from The University of Sydney Human Research Ethics Committee. Informed consent was not required. Additionally, each participating register received ethical and/or other approval to link data and provide deidentified data to the study, as required.

Results

The study included 4989 children with CP and 3684 children with sCHD born in the 6 regions within the birth years 1991-2009 (Figure 2). The total number of live births in the entire study sample was 1 734 612 (26% in 1991-1999 and 74% in 2000-2009), reflecting the data available from each participating region. Overall, the prevalence of sCHD was 2.1 per 1000 births (95% CI, 2.1-2.2).

Of the children with sCHD, 1.5% ($n = 57$) had a diagnosis of CP (15.5/1000 children with sCHD (95% CI, 11.7-20.0). In contrast, the prevalence of CP in the background population was 2.9 per 1000 live births (95% CI, 2.8-3.0). There was no significant difference in the proportion of children with sCHD that had a diagnosis of CP between the birth years 1991-1999 (12/1021 [1.2%]) and 2000-2009 (45/2663 [1.7%]) ($P = .26$).

Among children with sCHD, CP was classified as prenatally/perinatally acquired in 35 children (61%) and postneonatally acquired in 22 children (39%). This proportion of children with postneonatally acquired CP among children with sCHD (39%) was much higher than in children with CP without congenital anomalies (5%) ($P = .000$) (Figure 3). The proportion of children with postneonatally acquired CP was higher in birth years 1991-1999 compared

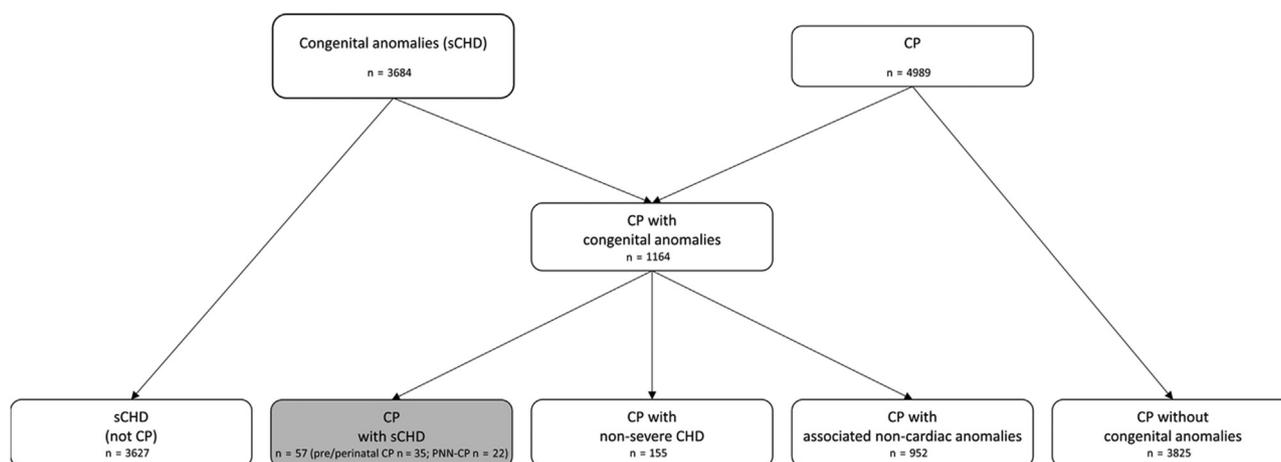


Figure 2. Study flowchart. PNN-CP, postneonatally acquired CP.

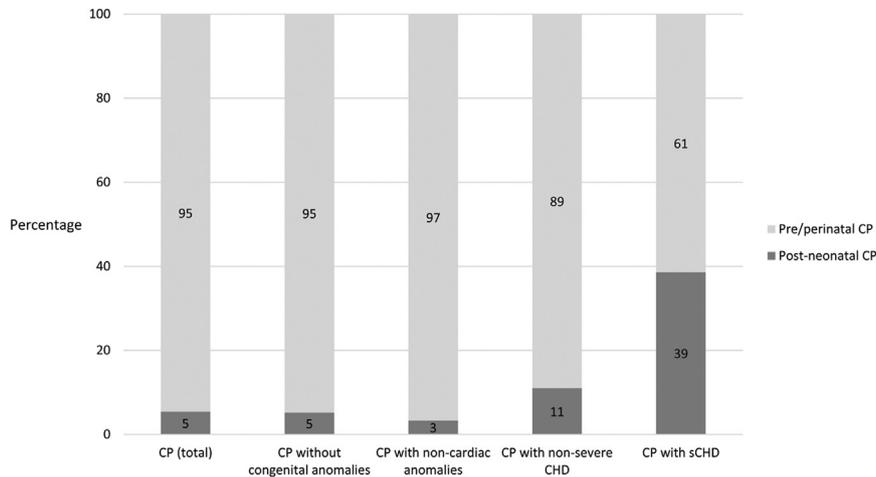


Figure 3. Percentage of prenatal/perinatal and postneonatal timing of CP for children with CP with and without congenital anomalies, born 1991-2009 in 6 regions of Europe and Australia.

with 2000-2009 (58% vs 33%), but the numbers were very small.

The birth characteristics of children in the study are presented in **Table I**, along with a comparison of children

with CP and sCHD and (a) children with sCHD (not CP), and (b) children with CP without congenital anomalies. The distribution of children small for gestational age at birth was the same across the groups. Children with sCHD

Table I. Birth characteristics of participants Distribution of demographic characteristics of children with congenital anomalies and children with CP born between 1991 and 2009 in 6 regions of Europe and Australia

Characteristics	CP with sCHD	sCHD (not CP)	CP with sCHD vs sCHD (not CP)	CP without congenital anomalies	CP with sCHD vs CP without congenital anomalies	CP with nonsevere CHD	CP with associated noncardiac anomalies
	No. (%)	No. (%)	P value	No. (%)	P value	No. (%)	No. (%)
Total	57	3627		3825		155	952
Isolated cardiac anomaly	36 (63)	2663 (73)	.082	-	-	97 (63)	-
Sex			.661		.882		
Male	32 (56)	2137 (59)		2183 (57)		77 (50)	540 (57)
Female	25 (44)	1484 (41)		1639 (43)		78 (50)	411 (43)
Unknown	0	6		3		0	1
Plurality			.116		.518		
Singleton	51 (91)	3454 (95)		3214 (88)		136 (88)	852 (91)
Multiple	5 (9)	163 (5)		427 (12)		19 (12)	85 (9)
Unknown	1	10		184		0	15
Gestational age, weeks			.006		.008		
<28	2 (4)	29 (1)		409 (11)		18 (12)	70 (8)
28-31	3 (5)	75 (2)		591 (16)		22 (14)	76 (8)
32-36	14 (25)	505 (15)		580 (16)		42 (27)	148 (16)
>37	38 (67)	2865 (82)		2044 (56)		73 (47)	635 (68)
Unknown	0	153		201			23
Birthweight, g			.031		.044		
<1000	2 (4)	29 (1)		387 (11)		16 (10)	73 (8)
1000-1499	4 (7)	83 (2)		449 (13)		17 (11)	63 (7)
1500-2499	8 (14)	483 (14)		707 (20)		45 (29)	165 (18)
>2499	43 (75)	2782 (82)		2039 (57)		76 (49)	627 (68)
Unknown	0	250		243		1	24
Small for gestational age centile (singletons only)							
<3rd	2 (4)	141 (4)	.999	144 (5)	.999	9 (7)	58 (7)
<10th*	5 (10)	329 (10)	.968	330 (11)	.912	17 (13)	132 (16)
≥10th	44 (90)	2840 (90)		2755 (89)		115 (87)	699 (84)
Unknown	2	285		129		4	21

Proportions are reported of known data only (excluding unknown/not collected).
*Small for gestational age centile: <10th centile also includes cases <3rd centile.

Table II. Distribution by subgroups of sCHDs among children with and without CP born between 1991 and 2009 in 6 regions of Europe and Australia

Subgroups	sCHD in all children (with and without CP)	sCHD in children without CP	sCHD in children with CP	% CP in children with sCHD (95% CI)
All sCHD	3684	3627	57	1.5 (1.2-2.0)
Q200: Common arterial trunk	91	86	5	5.5 (1.8-12.4)
Q201: Double outlet right ventricle	289	283	6	2.1 (0.8-4.4)
Q203: Transposition of great arteries	477	469	8	1.7 (0.7-3.3)
Q204, Q226, Q234: Univentricular heart defect*	417	408	9	2.2 (1.0-4.1)
Q212: Atrioventricular septal defect	530	527	3	0.6 (0.1-1.6)
Q213: Tetralogy of Fallot	568	558	10	1.8 (0.8-3.2)
Q220: Pulmonary valve atresia	280	272	8	2.9 (1.2-5.6)
Q224: Congenital tricuspid stenosis	212	208	4	1.9 (0.5-4.8)
Q225: Ebstein anomaly	73	73	0	0.0 (0.0-4.9) [†]
Q230: Congenital stenosis of aortic valve	383	378	5	1.3 (0.4-3.0)
Q232 & 233: Congenital mitral stenosis and congenital mitral insufficiency (mitral valve anomalies)	301	300	1	0.3 (0.0-1.8)
Q251: Coarctation of aorta	716	706	10	1.4 (0.7-2.6)
Q252: Atresia of aorta	31	31	0	0.0 (0.0-11.2) [†]
Q262: Total anomalous pulmonary venous connection	115	113	2	1.7 (0.2-6.1)

*Univentricular heart defect includes single ventricle, hypoplastic right heart syndrome and hypoplastic left heart syndrome.

[†]One sided, 97.5% CI.

and no CP were less likely to be born preterm overall than children with CP and sCHD, but the highest proportion of preterm births occurred in children with CP without congenital anomalies. For the children with CP and sCHD, 25% were born moderate preterm (gestational age of 32-36 weeks) compared with 15% of children with sCHD and no CP, and 16% of those with CP without congenital anomalies. Among the 57 children with CP and sCHD, 36 (63%) had isolated cardiac defects. Among the children with sCHD without CP, 73% had isolated cardiac defects ($P = .08$).

The distribution of type of sCHD and prevalence of CP is presented in Table II. The number of children in the specified groups of sCHD are small and CIs for the prevalence of CP are large. Children with common arterial trunk had the highest proportion of CP at 5.5% (5 of 91 children).

The clinical outcomes of children with CP and sCHD compared with all children with CP without congenital anomalies are presented in Table III. The CP subtypes differed ($P = .005$) between children with CP and sCHD and children with CP without congenital anomalies, with a greater proportion of unilateral spastic CP in children with sCHD. Intellectual impairment also differed ($P = .015$), with more impairment in children with CP and sCHD. When limiting to the smaller group of children with isolated sCHD compared with children without anomalies, GMFCS levels differed ($P = .028$) with a lower proportion of nonambulant CP (GMFCS IV-V); however, there was no significant difference in intellectual impairment. Within the group of children with CP and sCHD, those with the spastic bilateral CP subtype ($n = 21$) had more severe intellectual impairment (80% moderate to profound impairment) than those with spastic unilateral CP subtype ($n = 33$; none with moderate to profound intellectual impairment).

Information on the causes of CP was only available for the 22 children with postneonally acquired CP. For 64% of children (14/22), this factor was related to surgery for a CHD (acute hypoxia during surgery, cardiac arrest during surgery, cerebrovascular accident during surgery, encephalopathy, or severe postoperative complications after surgery); in 36% (8/22), the identified cause was cerebral infarction (no mention of surgery) and for 1 child it was due to unspecified cardiac arrest.

Discussion

This large European-Australian data linkage study showed that 1.5% of children born with sCHD were also diagnosed with CP. This proportion of CP is much higher than in the background live birth population, although the risk for the individual child remains low. Another important finding of the study is that 39% of children with CP and sCHD were classified as having postneonally acquired CP, much higher than the 6% among all children with CP.^{20,21}

Because both CP and sCHD are rare, there were only 57 children with a diagnosis of both CP and sCHD in this study despite the very large study sample covering 1.7 million births. The low number is likely not explained by underascertainment of liveborn children with sCHD in the congenital anomaly registries because the prevalence of sCHD in the study was 2.1 per 1000 births, which is comparable with the EUROCAT livebirth prevalence of nonchromosomal sCHD at 2.0 per 1000 births in 2000-2005.⁸ The overall prevalence of CP found in this study (1.5%) may be underestimated because mortality for children with sCHD is rather high within the first year after birth.²² Some children with sCHD may have died before the CP could have been diagnosed. In contrast, survival for children with sCHD has

Table III. Clinical outcomes for children with CP and sCHDs compared with children with CP without major congenital anomalies, born 1991-2009 in 6 regions of Europe and Australia

Outcomes	CP without congenital anomalies	CP with sCHD	CP with sCHD vs CP without congenital anomalies	CP with sCHD (isolated cardiac defects only)	CP with isolated sCHD vs CP without congenital anomalies
	No. (%)	No. (%)	<i>P</i> value	No. (%)	<i>P</i> value
Total	3825	57		36	
CP subtype			.005		.010
Bilateral spasticity	1822 (50)	21 (37)		11 (31)	
Unilateral spasticity	1357 (37)	33 (58)		23 (64)	
Spasticity (unknown)	26 (1)	0		0 (0)	
Dyskinesia	313 (9)	0 (0)		0 (0)	
Ataxia	155 (4)	3 (5)		2 (6)	
Unknown/other	152	0		0	
GMFCS			.184		.028
I-II	2267 (65)	40 (75)		29 (85)	
III	344 (10)	2 (4)		0	
IV-V	898 (26)	11 (21)		5 (15)	
Unknown	316	4		2	
Intellectual impairment			.015		.486
None	1931 (62)	21 (42)		17 (52)	
Mild	443 (14)	12 (24)		6 (18)	
Moderate to profound	754 (24)	17 (34)		10 (30)	
Unknown	697	7		3	
Vision impairment			.796		.758
None	2133 (65)	32 (63)		24 (71)	
Some	963 (29)	15 (29)		8 (24)	
Severe	186 (6)	4 (8)		2 (6)	
Unknown	543	6		2	
Hearing impairment			.408		.221
None	2907 (93)	45 (94)		29 (91)	
Some	122 (4)	3 (6)		3 (9)	
Severe	88 (3)	0 (0)		0	
Unknown	708	9		4	
Speech impairment			.374		.762
None	1441 (45)	18 (35)		14 (42)	
Some	1070 (34)	20 (39)		13 (39)	
Severe	682 (21)	13 (25)		6 (18)	
Unknown	632	6		3	
Epilepsy			.195		.250
No	2288 (68)	31 (60)		20 (59)	
Yes	1073 (32)	21 (40)		14 (41)	
Unknown	464	5		2	

increased over the last decades, which may explain our finding of an apparently higher prevalence of CP for the children with sCHD born in 2000-2009.^{22,23}

Children with CP and sCHD generally had less severe CP subtypes than children with CP without congenital anomalies, with a higher proportion with unilateral spastic CP more often caused by neonatal stroke.²⁴ Among those with isolated sCHD, better gross motor function was also seen. There were no children with dyskinetic CP among the 57 children with sCHD, meaning injuries to the basal ganglia are very rare for these children. However, children with CP and sCHD had more overall intellectual impairments than children with CP without anomalies. The association between sCHD and intellectual impairment is well-described in the literature for children with sCHD in general.^{11,25} It is unclear whether this finding is solely related to fetal development, or whether cardiac surgery and the intensive care unit before and after surgery plays a role, given the association between anesthesia early in life and lower academic performance later in life.²⁶

Studies describing the epidemiology and etiology of CP traditionally explore children with prenatal/perinatal CP and postneonatal CP separately. However, when sCHD lies on causal pathways to CP, the brain injury may occur in either the prenatal/perinatal or postneonatal period or in both. In this study, the brain injury occurred in the prenatal/perinatal period for 61% of children. This finding is in line with the comprehensive literature on cerebral magnetic resonance imaging before and after surgery for infants with sCHD, documenting that a high proportion of infants (24%-39%) have abnormal imaging before the surgery.^{9,12} Similarly, a meta-analysis published in 2015 concluded that the neurodevelopmental delays in children with sCHD were mainly due to prenatal brain injuries and not related to the cardiac surgery.¹¹ By contrast, 39% of children had a brain injury that occurred in the postneonatal period, and in 64% of these the injury was known to be directly related to cardiac surgery.

During the 19 years of the study period, there have been improvements in the treatment of children with sCHD,

including a higher prenatal detection rate; improved care before, during, and after the cardiac surgery; and more focus on preventing failure to thrive.^{23,27-29} These improvements are expected to decrease the risk of cerebral complications and developmental delays for these children. A European study including children born in 1995-2014 showed that length of stay in hospitals for children with sCHD up to age 5 years were much longer than the expected hospital stays related to the surgeries.²⁸ It remains to be seen whether improvements in care over time have an impact on the association between CP and sCHD, and future research should consider this in more recent birth cohorts.

Earlier detection of CP is now possible for infants from 3 months of age, through the use of the assessments including General Movements Assessment (including in a surgical population) and cerebral magnetic resonance imaging.^{30,31} General Movement Assessment screening of all infants with sCHD should be considered.

The main strength of this study is the use of data from population-based registries with validated and standardized data. The multicenter study also used data from 2 continents, allowing for an analysis of the rare event of children having both CP and sCHD. The main limitation of the study is that the inclusion of births over a 20-year period was needed to have enough children to perform analyses. However, the numbers were too small for comparisons between the 2 time periods for some of the outcomes. It is also a limitation that the Danish CP registry does not include children with postneonally acquired CP; therefore, the results of postneonally acquired CP are at minimum (but likely had only a small impact on the overall findings, because the Danish sample was small). Owing to limitations on available data, the study did not include information on pregnancy risk factors and mode of delivery, which may differ among the group of children with sCHD with and without CP. Future research will benefit from the increasing availability of cerebral magnetic resonance imaging and genomic findings for children with CP and sCHD, all of which may help to elucidate specific causal pathways to CP that include sCHD. Finally, because this study included data from high-income countries only, findings cannot be extrapolated to low- and middle-income settings where the incidence of and care and survival for children with sCHD differs greatly.³²

In high-income countries, children with sCHD have a 5 times higher prevalence of CP compared with the prevalence in the general population. Clinical outcomes are less severe in children with CP and sCHD compared with children with CP without congenital anomalies. A higher proportion of children with CP and sCHD have postneonally acquired CP. ■

Declaration of Competing Interest

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The authors declare no conflicts of interest.

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