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ORIGINAL ARTICLE

Postneonatal Cerebral Palsy in Europe: Prevalence and Clinical Characteristics According to Contributory Events: An SCPE Study

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ABSTRACT

Background: Postneonatal cerebral palsy (PNCP) is rare and requires large databases to be studied over time.

Objectives: To study the time trend of prevalence of PNCP overall and by cause, and to describe the clinical characteristics of children with PNCP according to cause and compared with children with pre/peri/neonatal CP (PPNCP).

Methods: The Surveillance of Cerebral Palsy in Europe (SCPE) database was used. Primary events (the first known chronological event in the causal chain) were classified according to the SCPE classification (six main and 19 sub-categories). Prevalence trends for children born during 1976–2012 were modelled using multilevel generalised linear models. The clinical characteristics of PNCP and PPNCP cases born after 1998 were reported as proportions.

Results: The prevalence rates of PNCP were 1.76 (95% confidence interval (CI) 1.37, 2.23) and 0.82 per 10,000 live births (95% CI 0.73, 0.92) in children born during 1976–1980 and 2006–2012, respectively. The models showed a 2% annual decline in overall prevalence (prevalence rate multiplied by 0.98 each year) and a 10% decline for infectious causes for every 5-year change. The prevalence rate in children born during 2006–2012 was 0.26 per 10,000 (95% CI 0.21, 0.32) for infectious causes, which remained the most frequent. No trend emerged for other causes. Unilateral spastic CP, associated impairments and severe gross motor dysfunction were more frequent in PNCP than in PPNCP, and PNCP showed predominantly grey matter injury (55.6%). Seventeen percent were born preterm. PNCP differed by cause, with cerebrovascular accidents presenting the least severe and hypoxic causes the most severe forms.

Conclusion: Our study confirms the decrease in the prevalence of PNCP in children born up to 2012, particularly for CP, due to infectious causes, which remain the most frequent. Children with PNCP had more severe presentation overall than those with PPNCP, with severity depending on the cause.

1 | Background

Cerebral palsy (CP) is characterised by permanent disorders of movement and/or posture and of motor function due to non-progressive damage to the developing brain [1]. Postneonatal CP (PNCP) differs from pre- and peri-neonatal CP (PPNCP) by the timing and the nature of the causal event leading to brain injury. Brain damage occurring in the postneonatal period (i.e. from more than 28 days after birth until the age of 2 years) affects a small proportion of children with CP, around 4% to 7% in high-income countries for the most recent generations studied (children born up to 2012) [2–5], which is less than for earlier generations [6, 7].

The situation is radically different in low- and middle-income countries, where postneonatal CP accounts for more than a third of cases in some countries [8, 9]. A decline in the prevalence of PNCP has been observed in high-income countries [3, 4] and confirmed for children born up to 1998 by the Surveillance of Cerebral Palsy in Europe network (SCPE) [10]. In addition, children with PNCP have been described as having more severe motor impairments and more comorbidities than children with PPNCP [3, 4, 11]. For PNCP, the various events involved in the aetiological pathways leading to brain injury are often clearly identified. However, no consensus emerges in the literature to indicate which of these events should be selected as the primary event. Moreover, the classifications used lack homogeneity, making it challenging to compare time trends in even the broadest categories of causes. The SCPE network recently presented its classification of these events, along with guidelines on how to designate and code the main primary event to be reported. This is defined as the first chronological event in the possibly complex pathway leading to CP [12]. This detailed two-level classification describes potentially preventable events using six major categories: (A) infections; (B) head injuries (accidental or non-accidental); (C) brain injuries related to surgery or other invasive medical interventions; (D) all non-traumatic events, ischaemic, haemorrhagic or unspecified cerebrovascular accidents (CVA); (E) hypoxic brain damaging events of other origin; and (F) miscellaneous.

Consistent use of this classification for all cases of PNCP recorded in the SCPE database makes it possible to monitor prevalence by causes over time to help to guide and/or adapt preventive measures. Describing the nature and severity of impairments and comorbidities could help provide individualised care and prevention. The aims of our study were (1) to investigate changes over time in the prevalence of PNCP overall and according to the major categories of primary events using the SCPE database, and (2) to describe the clinical characteristics of children with PNCP according to the main categories of primary events, and to compare these clinical characteristics with those of children with PPNCP.

2 | Methods

2.1 | Source of Data and Study Population

The data were obtained from the database of the Surveillance of Cerebral Palsy in Europe network of population-based CP

registries in Europe. The list of registries involved and years of birth available for the various analyses presented below are shown in Table S1. Children with CP were eligible for this study if their mothers lived in an area covered by a contributing registry at birth (except for the two French registries). Complete data for children born in 2013 were unavailable for some registries, which could bias the prevalence estimates but does not alter the description of the variables studied. Therefore, prevalence rates were not estimated after 2012.

2.2 | Study Variables

The primary event (the first known event in chronological order involved in the pathway leading to the brain injury and considered a point of origin) was classified into six main and 19 sub-categories according to the SCPE classification [12]. All cases were reviewed by at least two authors to ensure standardised classification of the primary event for all generations. The other variables studied were sex, age at onset of brain injury (1–12 months vs. 13–24 months), preterm birth (before 37 weeks of gestation), low birth weight (<2500 g), admission to a neonatal care unit (NCU) at birth, cardiac malformations (data only available for birth years 2009 onwards), CP subtype (bilateral spastic, unilateral spastic, other forms: dyskinetic, ataxic, unclassified), gross motor function (according to GMFCS levels: [13] GMFCS I–III vs. GMFCS IV–V), severe intellectual impairment (IQ < 50), visual or hearing impairment, associated epilepsy (with or without current treatment) and speech disorders assessed with the Viking Speech Scale (VSS) [14] for children born in 2007 and later (severe speech disorder, VSS score 3–4, vs. not severe, VSS score 1–2). Children with GMFCS IV–V or IQ < 50 were considered as having severe impairment, while very severe impairment was defined as GMFCS IV–V and IQ < 50. Postneonatal MRI results were available for children born from 2007 onwards and were classified using the MRI classification system (MRICS) [15] as (A) maldevelopments, (B) predominant white matter injury, (C) predominant grey matter injury, (D) miscellaneous and (E) normal.

2.3 | Statistical Analysis

2.3.1 | Time Trend in Prevalence of PNCP

All children with PNCP born from 1976 to 2012 were considered. The overall prevalence of PNCP and severe PNCP was calculated per 10,000 live births, counting cases with a known or unknown primary event. Prevalence rates were also calculated by the main category of primary event. Registry data were considered if (1) the average annual number of live births in the registry surveillance area was > 3000, (2) the registry contributed data for at least 5 years and (3) the corresponding denominators were available.

The Kendall's tau rank correlation coefficient between year of birth and prevalence rate was calculated in each registry. The time trends were then modelled using multilevel generalised linear regression models with a log link and an offset term equal to the log of the number of live births. The number of PNCP cases was entered as the dependent variable. A random intercept for

the registry allowed data to be nested within registries. Overdispersion was investigated by comparing the Poisson with the negative binomial null models. The model with the lowest AIC value was selected.

To examine the overall PNCP prevalence time trend, the prevalence change for a one-year increase was modelled with a linear trend, or restricted cubic splines (RCS) [16] that allowed for a more flexible trend. Using RCS consisted in modelling the time variable by using piecewise functions (here, cubic spline functions). We estimated three models with RCS, varying the number of knots between three and five equally spaced knots, which means that flexible smoothed non-monotonic time trends were fitted with two to four splines over the time period.

To examine the time trends by the main category of primary event, data were combined over 5-year periods. The prevalence change for a one-period increase was modelled with a linear time effect, RCS with three knots, or with a discrete time effect with time periods being modelled by indicator variables.

For all analyses, the best functional form for the time trend was chosen according to the AIC value. A random slope was added in the final models in order to test for heterogeneity of trends between registries.

Analyses were carried out using Stata 18 software.

2.3.2 | PNCP Cases According to Primary Event and Comparison With PPNC

Analysis was restricted to children born during 1998–2013.

2.3.3 | Missing Data

In analyses of prevalence trends between 1976 and 2012, missing data on the primary event were not replaced. Children with CP of unknown primary event were included in overall prevalence trend models. They were excluded from time trend analyses by primary event category.

In analysis of the characteristics of CP cases born between 1998 and 2013, missing data ranged from 0% for 'sex' to 18.8% for 'admission to NCU'. For this analysis, missing data were multiply imputed using the multiple imputations by chained equations (MICE) algorithm with 50 imputations performed separately for PNCP and PPNC cases. In the PNCP imputation model, the main category of primary event was considered and imputed. A logistic regression model was used for imputing binary variables, and a multinomial model was used for imputing categorical variables. Missing data on classification of brain imaging results were not imputed due to insufficient numbers in certain categories. Proportions were estimated within each of the imputed datasets and pooled using Rubin's rules. Proportions were presented with their 95% confidence interval (CI).

Ethics Statement

This study was based on pseudonymised registry data compiled at the European level in the SCPE database. It did not require any contact with the registered persons, and no ethical review or approval was required.

4 | Results

4.1 | Prevalence of PNCP

A total of 17 registries contributed to the prevalence analyses, corresponding to 812 children with PNCP born during 1976–2012. The primary event remained unknown or unclassifiable in 63 (7.8%) cases. More specifically, 70% of these unclassifiable events originated from a single registry which did not record the causes of PNCP before 1984. The stability of the results of the time trend analyses was assessed in sensitivity analysis by performing the statistical models after exclusion of the data collected in this registry for the 1976–1984 period.

Table 1 presents prevalence rate estimates during the study period for seven birth periods. The prevalence rates of PNCP overall ranged from 1.76 (95% CI 1.37, 2.23) to 0.82 (95% CI 0.73, 0.92) cases per 10,000 live births in children born during 1976–1980 and 2006–2012, respectively. The prevalence rates of severe PNCP ranged from 1.01 (95% CI 0.72, 1.38) to 0.41 (95% CI 0.34, 0.48) for the same periods.

Kendall's tau coefficients were < -0.25 in 11 registries, between -0.25 and 0.25 in seven registries and > 0.25 in one registry (indicating a monotonic upward trend). Because of convergence issues, random slope models were not estimated and so we could not assess and consider heterogeneity in time trends among registries. We thus excluded the only registry with a clear upward trend from the time trend analyses. For sensitivity analysis, models were re-run, including data from this registry to evaluate the impact of this exclusion.

The results of time trend analysis, for the prevalence of PNCP overall and by the main category of primary event, are displayed in Table S2, for the primary analysis as well as for sensitivity analyses. Observed and fitted trends are displayed in Figures 1 and 2. For each one-year increase, the fitted prevalence rate of PNCP overall was multiplied by 0.98 (95% CI 0.97, 0.99), indicating an annual decline in prevalence of 2%. The sensitivity analyses confirmed the main analysis.

The fitted prevalence rate for infections (category A) decreased by 10% between each 5-year period (prevalence rate ratio = 0.90, 95% CI 0.81, 0.99). No trend emerged for aetiologies B, C, D and F. For aetiology E-hypoxia, the AIC values indicated that the trend was better modelled using a discrete time effect. The prevalence rate (PR) was higher during the 1986–1990 period (PR ratio = 3.75 (95% CI 1.80, 7.79) vs. the last period).

TABLE 1 | Number of cases recorded and birth prevalence rate (PR) of postneonatal cerebral palsy (PNCP) in children born during 1976–2012 in Europe, according to the primary event (i.e. the first known chronological event in the causal chain). Data from 17 registries from the Surveillance of Cerebral Palsy in Europe network.

Year of birth	Number of live births	PNCP of all causes (including unknown causes)			PNCP of cause A (Infection)			PNCP of cause B (Head injury)			PNCP of cause C (Brain injury related to surgery)			PNCP of cause D (Cerebrovascular accident)			PNCP of cause E (Hypoxic)			PNCP of cause F (Miscellaneous)						
		<i>N</i>	<i>n</i>	(<i>n</i> ^a)	PR ^b	CI ^c	<i>n</i>	PR ^b	CI ^c	<i>n</i>	PR ^b	95% CI ^c	<i>n</i>	PR ^b	95% CI ^c	<i>n</i>	PR ^b	95% CI ^c	<i>n</i>	PR ^b	95% CI ^c	<i>n</i>	PR ^b	95% CI ^c		
All PNCP cases																										
1976–1980	386, 207	68	(24)	1.76	(1.37, 2.23)	24	0.62	(0.40, 0.92)	9	0.23	(0.11, 0.44)	6	0.16	(0.06, 0.34)	1	0.03	(0.00, 0.14)	3	0.08	(0.02, 0.23)	1	0.03	(0.00, 0.14)	1	0.03	(0.00, 0.14)
1981–1985	575, 991	95	(24)	1.65	(1.33, 2.02)	37	0.64	(0.45, 0.89)	9	0.16	(0.07, 0.30)	9	0.16	(0.07, 0.30)	8	0.14	(0.06, 0.27)	3	0.05	(0.01, 0.15)	5	0.09	(0.03, 0.20)	5	0.09	(0.03, 0.20)
1986–1990	604, 800	84	(6)	1.39	(1.11, 1.72)	39	0.64	(0.46, 0.88)	7	0.12	(0.05, 0.24)	8	0.13	(0.06, 0.26)	5	0.08	(0.03, 0.19)	16	0.26	(0.15, 0.43)	3	0.05	(0.01, 0.14)	3	0.05	(0.01, 0.14)
1991–1995	497, 199	44	(1)	0.89	(0.64, 1.19)	15	0.30	(0.17, 0.50)	5	0.10	(0.03, 0.23)	8	0.16	(0.07, 0.32)	8	0.16	(0.07, 0.32)	5	0.10	(0.03, 0.23)	2	0.04	(0.00, 0.15)	2	0.04	(0.00, 0.15)
1996–2000	857, 559	70	(4)	0.82	(0.64, 1.03)	23	0.27	(0.17, 0.40)	18	0.21	(0.12, 0.33)	10	0.12	(0.06, 0.21)	10	0.12	(0.06, 0.21)	1	0.01	(0.00, 0.06)	4	0.05	(0.01, 0.12)	4	0.05	(0.01, 0.12)
2001–2005	1, 905, 974	162	(0)	0.85	(0.72, 0.99)	71	0.37	(0.29, 0.47)	22	0.12	(0.07, 0.17)	26	0.14	(0.09, 0.20)	26	0.14	(0.09, 0.20)	11	0.06	(0.03, 0.10)	6	0.03	(0.01, 0.07)	6	0.03	(0.01, 0.07)
2006–2012	3, 530, 642	289	(4)	0.82	(0.73, 0.92)	92	0.26	(0.21, 0.32)	67	0.19	(0.15, 0.24)	46	0.13	(0.10, 0.17)	40	0.11	(0.08, 0.15)	24	0.07	(0.04, 0.10)	16	0.05	(0.03, 0.07)	16	0.05	(0.03, 0.07)
Severe PNCP cases ^d																										
1976–1980	386, 207	39	(16)	1.01	(0.72, 1.38)	12	0.31	(0.16, 0.54)	4	0.10	(0.03, 0.27)	4	0.10	(0.03, 0.27)	1	0.03	(0.00, 0.14)	2	0.05	(0.01, 0.19)	0	0.00	(0.00, 0.10)	0	0.00	(0.00, 0.10)
1981–1985	575, 991	48	(10)	0.83	(0.61, 1.11)	23	0.40	(0.25, 0.60)	3	0.05	(0.01, 0.15)	6	0.10	(0.04, 0.23)	2	0.03	(0.00, 0.13)	1	0.02	(0.00, 0.10)	3	0.05	(0.01, 0.15)	3	0.05	(0.01, 0.15)
1986–1990	604, 800	47	(3)	0.78	(0.57, 1.03)	24	0.40	(0.25, 0.59)	3	0.05	(0.01, 0.14)	1	0.02	(0.00, 0.09)	1	0.02	(0.00, 0.09)	13	0.21	(0.11, 0.37)	2	0.03	(0.00, 0.12)	2	0.03	(0.00, 0.12)
1991–1995	497, 199	30	(0)	0.60	(0.41, 0.86)	12	0.24	(0.12, 0.42)	3	0.06	(0.01, 0.18)	5	0.10	(0.03, 0.23)	4	0.08	(0.02, 0.21)	4	0.08	(0.02, 0.21)	2	0.04	(0.00, 0.15)	2	0.04	(0.00, 0.15)
1996–2000	857, 559	34	(2)	0.40	(0.28, 0.55)	12	0.14	(0.07, 0.24)	8	0.09	(0.04, 0.18)	3	0.03	(0.01, 0.10)	5	0.06	(0.02, 0.14)	1	0.01	(0.00, 0.06)	3	0.03	(0.01, 0.10)	3	0.03	(0.01, 0.10)

(Continues)

TABLE 1 | (Continued)

Year of birth	Number of live births	PNCP of all causes (including unknown causes)		PNCP of cause A (Infection)		PNCP of cause B (Head injury)		PNCP of cause C (Brain injury related to surgery)		PNCP of cause D (Cerebrovascular accident)		PNCP of cause E (Hypoxic)		PNCP of cause F (Miscellaneous)	
		<i>N</i>	<i>n</i>	<i>n</i>	PR ^b 95% CI ^c	<i>n</i>	PR ^b 95% CI ^c	<i>n</i>	PR ^b 95% CI ^c	<i>n</i>	PR ^b 95% CI ^c	<i>n</i>	PR ^b 95% CI ^c	<i>n</i>	PR ^b 95% CI ^c
2001–2005	1,905,974	85	(0)	47	0.25 (0.18, 0.33)	13	0.07 (0.04, 0.12)	10	0.05 (0.03, 0.10)	6	0.03 (0.01, 0.07)	8	0.04 (0.02, 0.08)	1	0.01 (0.00, 0.03)
2006–2012	3,530,642	143	(0)	50	0.41 (0.34, 0.48)	34	0.10 (0.07, 0.13)	23	0.07 (0.04, 0.10)	8	0.02 (0.01, 0.04)	15	0.04 (0.02, 0.07)	13	0.04 (0.02, 0.06)

Note: The number of registries included in prevalence rate calculation differs from year to year, due to the fact that each registry collected data on PNCP cases over different time periods.

^aPNCP of unknown causes.

^bPR prevalence rate per 10,000 live births.

^cCI confidence interval.

^dSevere PNCP defined as Gross Motor Function Classification System IV-V or intellectual quotient < 50.

4.2 | Primary Events Between 1998 and 2013

Table 2 presents the distribution of cases born during 1998–2013 according to the main category and sub-categories. Infectious events represented 36.4% of cases and remained the most frequent.

4.3 | PNCP Cases According to Primary Event and Comparison With Children With PPNCB Born During 1998–2013

Figure 3 describes clinical characteristics of children with PNCP born during 1998–2013 according to primary event. Table 3 presents the clinical characteristics of PNCP and PPNCB cases. Age at onset of injury was ≤12 months in most cases (76.7%). The injury occurred more frequently after 12 months for categories D-CVA (32.8%) and E-Hypoxic (36.3%) than for the other categories. No sex difference was observed. Preterm births, low birth weight and NCU admissions were less frequent in PNCP than in PPNCB. In children with PNCP, preterm birth rate differed according to primary event, with the highest proportion in category A-Infection (25.7%).

Compared with children with PPNCB, children with PNCP were more likely to present cardiac malformations, unilateral spastic CP subtype, associated impairments (except hearing impairments) and comorbidities, and more severe gross motor dysfunction.

Clinical characteristics also differed according to the primary event reported for children with PNCP (Figure 3). Cardiac malformations were reported in over half of category C-Related to surgery cases. We observed a greater frequency of unilateral spastic forms in category D-CVA (70.3%) and, to a lesser extent, in category C-Related to surgery (59.1%) compared with the other categories, whereas bilateral spastic forms were most frequent in category E-Hypoxic (64.1%). Severe and very severe forms of CP were most frequent in category E-Hypoxic (68.8% and 56.8%, respectively) and least frequent in category D-CVA (27% and 11%). The proportion of visual impairment ranged from 33% (category D-CVA) to 71.4% (category B-Head injury). Hearing impairment was most frequent in category A-Infection (13.3%). The proportion of epilepsy was lowest in category C-Related to surgery but still concerned just over half the children. The proportion of severe speech disorders was lowest in category D-CVA, while it exceeded 60% in categories A-Infection, E-Hypoxic and F-Miscellaneous.

MRI findings differed between PNCP and PPNCB. For PNCP, predominant grey matter injuries were most frequent, whereas for PPNCB, predominant white matter injuries were most frequently reported. Among children with PNCP, findings differed according to primary event. Grey matter injury predominated in categories D-CVA (80.6%) and E-Hypoxic (75%), the proportion of MRIs classified as miscellaneous was lowest for category E-Hypoxic (10%) and highest for category F-Miscellaneous (54.5%), while normal MRI findings were highest for category F-Miscellaneous (18.2%).

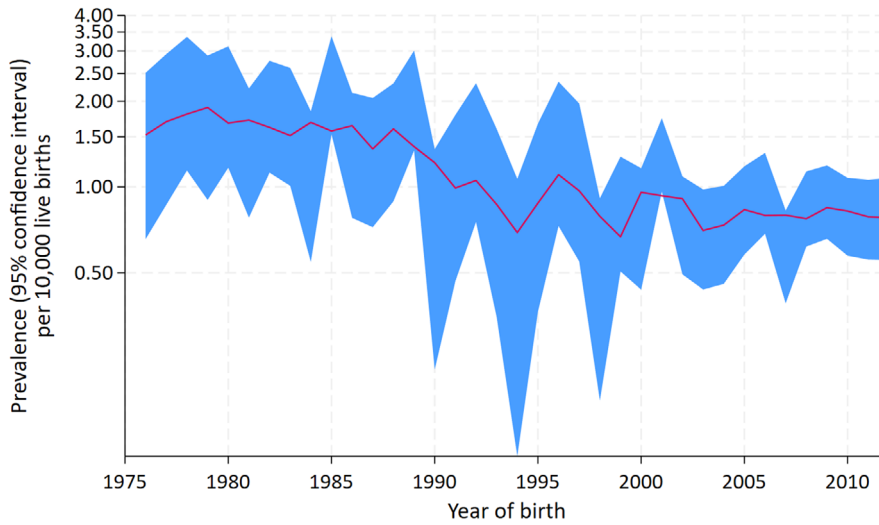


FIGURE 1 | Birth prevalence rate (PR) of postneonatal CP per 10,000 live births: Observed data and fitted PRs predicted from the negative binomial random intercept model with a linear time trend. The fitted PR considers the fixed part of the model (random intercept = 0). Registry C32A was excluded from the analysis.

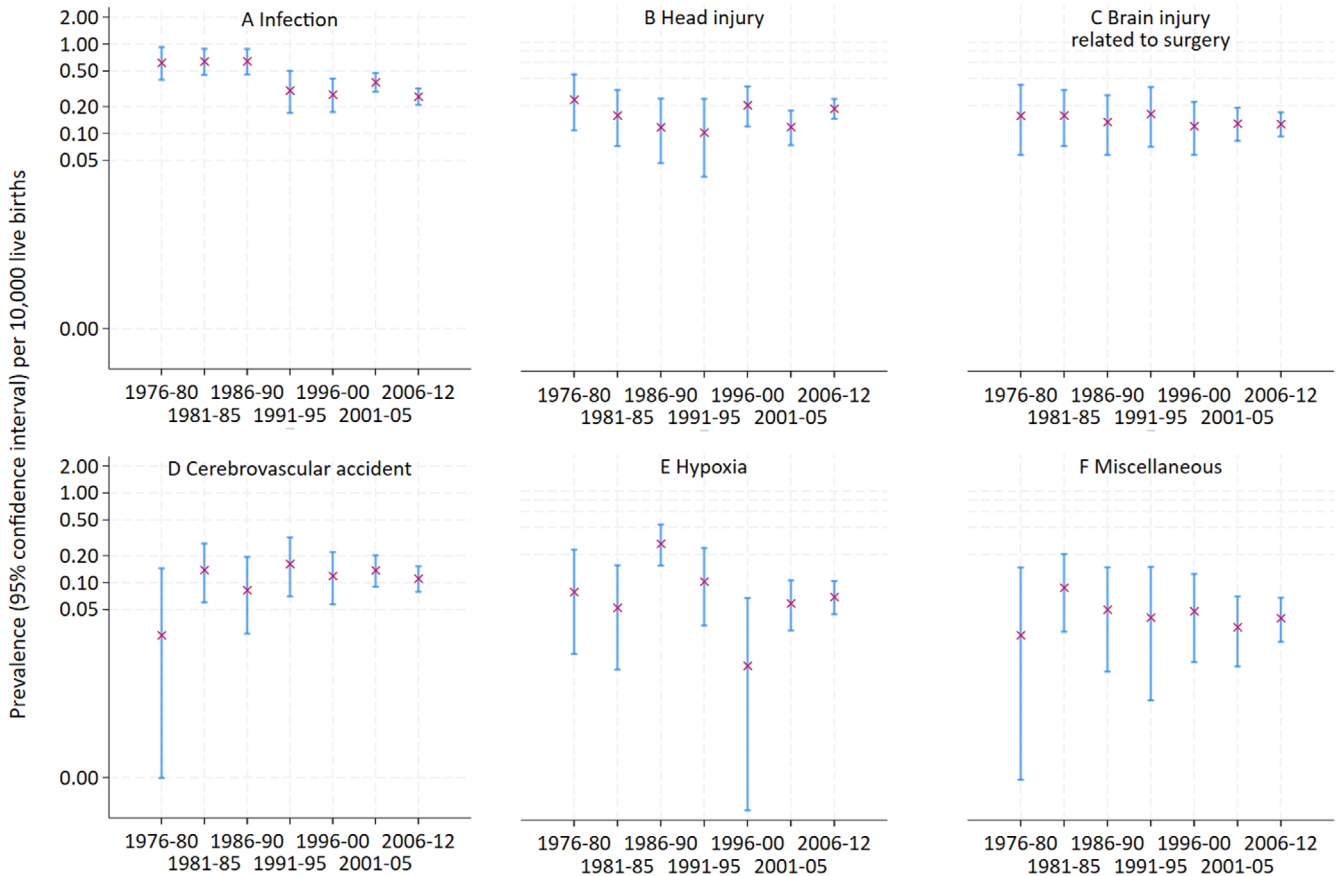


FIGURE 2 | Birth prevalence rate (PR) of postneonatal CP per 10,000 live births: Observed data and fitted PRs predicted from the random intercept regression models, by cause. The fitted PR considers the fixed part of the model (random intercept = 0). Registry C32A was excluded from the analysis.

TABLE 2 | Distribution of cases according to the SCPE classification of primary event for 524 children with PNCP with known primary event born between 1998 and 2013.

Year of birth	1998–2013	
	N	%
A Infection	191	36.4
A1 Encephalitis (all origins, except autoimmune origin) and/or meningitis (bacterial, viral, fungal ...)	136	26.0
A2 Severe sepsis, septicaemia or septic shock	13	2.5
A3 Other infections and consequences (Reye syndrome, gastroenteritis with severe dehydration, respiratory infections, malaria, encephalopathies with [suspected] infectious origin...)	42	8.0
B Head injury	109	20.8
B1 Road traffic accident	16	3.1
B2 Other accidental injury	17	3.2
B3 Non-accidental injury	41	7.8
B4 Unspecified	35	6.7
C Brain injury related to surgery or other medical intervention	80	15.3
C1 Cardiac	45	8.6
C2 Brain	20	3.8
C3 Other organs	6	1.1
C4 Unspecified	9	1.7
D Cerebrovascular accident	80	15.3
Non-traumatic (including ischaemic, haemorrhagic or unspecified cerebrovascular accident)		
E Hypoxic brain damaging event of other origin	39	7.4
E1 Near-miss sudden death syndrome	3	0.6
E2 Near-drowning	11	2.1
E3 Respiratory distress syndrome of non-infectious origin (traumatic or related to foreign body in respiratory tract ...)	5	0.9
E4 Cardiac arrest and heart infarction	15	2.9
E5 Hypoxic of other origin (carbon monoxide inhalation, hypoglycaemic coma, electrocution ...) or unspecified	5	0.9
F Miscellaneous	25	4.8
F1 Status epilepticus, convulsions	15	2.9
F2 Other	10	1.9
Total with known primary event	524	100

5 | Comment

5.1 | Principal Findings

The overall prevalence of PNCP and the prevalence of PNCP with infectious primary events decreased between 1976 and 2012. Infections remained the most frequent primary event. PNCP cases were more severe than PPNCP and severity differed according to cause.

5.2 | Strengths of the Study

One of the strengths of this study lies in the use of a valid tool to classify the causal events of CP in a homogeneous way. Use

of the SCPE database allows solid comparisons between PNCP and PPNCP cases using similar definitions and severity thresholds over the same registries and study periods. Lastly, the brain imaging data make an essential contribution that is rare in the literature.

5.3 | Limitations of the Data

Although the SCPE database provides information at the European level, the low number of PNCP cases remains a major limitation in analyses carried out by type of cause and prevents trend analysis by sub-category. Because of lack of information on the type of germ involved in infections, we could not distinguish between vaccine-preventable and

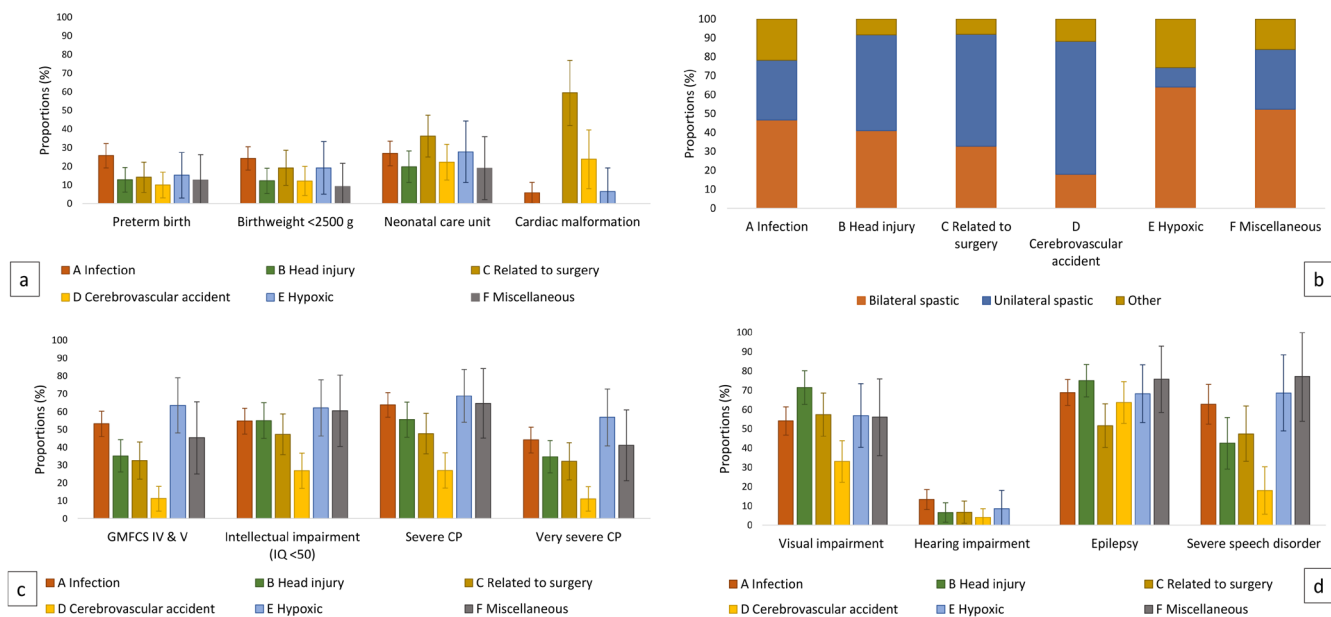


FIGURE 3 | Neonatal characteristics (a), type of CP (b), severity of motor and intellectual impairments (c) and associated impairments (d) of children born during 1998–2013 with postneonatal CP according to the main categories of classification of primary event involved in brain lesion. Percentages and 95% CI are based on imputed data.

non-vaccine-preventable infectious causes. Missing data on causes remained low but could have led to slight underestimation of prevalence by main categories. Registries vary in geographical and temporal coverage. We took account of this potential centre effect in prevalence trend analyses. Nevertheless, the validity of our estimates relies on the assumption that, each year, the registries with available data constitute a representative sample of European regions.

5.4 | Interpretation

The overall annual decline in prevalence was 2% with a prevalence of 0.82 per 10,000 for children born in 2012, similar to that described for other high-income countries [17]. A similar trend was found in both Victoria and Western Australia over a comparable study period [4]. Previous publications have shown a decrease in prevalence for children born before 2000 [7, 10], including for PNCP of infectious origin. These trends therefore appear to continue at least until the generation of children born in 2012, while no trends were found for PNCP with other causes. Nevertheless, infections remained the most frequent primary event (36.4% of cases born after 1998). This finding differs from what has recently been described in the Australian Cerebral Palsy Register (ACPR) network for similar generations, where infections accounted for only one-quarter of cases and CVAs were the most frequent cause [4]. However, causal events were not identically reported in the two networks. In the SCPE network, the earliest event in the causal chain, called the primary event, is reported, in order to identify opportunities for prevention. In the Australian ACPR network, historically prior to harmonisation with the SCPE classification, the PNCP event understood to be responsible for the brain injury, usually the most proximal event, was recorded. Thus, PNCP cases resulting from a non-infectious proximal event that followed an infection would have been

classified as an infection in the SCPE classification and not in the ACPR. This may explain the lower proportion of PNCP cases with an infectious origin in the ACPR compared with the SCPE network. In addition, the CVA category of the ACPR includes CVAs associated with surgery (10% of cases), whereas in the SCPE classification these situations are categorised as a different main category (C-Events associated with surgery or medical intervention). Combining categories C and D-CVA of the SCPE classification results in 30.6% of cases born from 1998 onwards, close to the 33% in the CVA category of the Australian network. Nevertheless, a clear reduction in the proportion of infectious causes was reported in both networks and could be linked to the vaccination campaigns introduced in Europe against haemophilus around 1993 and against pneumococcus in the early 2000s, leading to an overall reduction in bacterial meningitis and invasive infections [18–20]. Within the EU, vaccination strategies vary between countries, but the same level of protection is guaranteed in every country [21]. For non-infectious primary events, no prevalence trends were observed. In particular, there was no downward trend in traumatic events despite the road safety campaigns implemented, maybe because the number of serious injuries following road accidents has fallen at a slower rate than the number of deaths [22]. More generally, trend analysis by sub-category would be necessary to interpret these trends more precisely.

As expected, among PNCP cases, the proportion of children born preterm or with low birth weight was much lower than among PNNCP cases. Moreover, the proportion of preterm births or birth weights < 2500 g was much higher (17.4% and 18%) among PNCP cases than in the general population in Europe, where the percentage of live births with birth weight < 2500 g ranged from 3.4% to 9.8% and the preterm birth rate varied from about 5% to 10% [23]. This over-representation in PNCP of children born preterm or with low birth weight has

TABLE 3 | Description of the characteristics of the children born during 1998–2013 with postneonatal CP compared with children with pre/peri/neonatal CP. Numbers are presented before imputation while percentages, and 95% CI are based on imputed data unless otherwise stated.

	Total postneonatal CP		Total pre/peri/neonatal CP	
	N = 533		N = 10,219	
	<i>n</i>	% (95% CI)	<i>n</i>	% (95% CI)
Sex male	297	55.7 (51.5, 59.9)	5955	58.3 (57.3, 59.2)
Missing	0		3	
Preterm birth (<37 weeks)	82	17.4 (14.0, 20.8)	4779	48.6 (47.6, 49.6)
Missing	62		439	
Birth weight < 2500 g	83	18.0 (14.5, 21.5)	4653	48.5 (47.5, 49.5)
Missing	86		751	
Neonatal care unit	109	25.8 (21.8, 29.8)	6375	69.7 (68.7, 70.7)
Missing	100		1217	
Cardiac malformation^a	31	15.5 (10.5, 20.6)	137	4.1 (3.4, 4.8)
Missing	12		246	
Type of motor function				
Bilateral spastic	216	40.5 (36.4, 44.7)	5346	52.3 (51.4, 53.3)
Unilateral spastic	235	44.1 (39.9, 48.3)	3318	32.5 (31.6, 33.4)
Other	82	15.4 (12.3, 18.5)	1552	15.2 (14.5, 15.9)
Missing	0		3	
GMFCS IV & V (not able to walk)	209	40.2 (36.0, 44.4)	3000	30.3 (29.4, 31.2)
Missing	9		271	
Intellectual impairment (IQ < 50)	235	50.2 (45.8, 54.6)	2805	31.7 (30.8, 32.7)
Missing	62		1294	
Severe CP^b	276	54.4 (50.0, 58.7)	3862	39.8 (38.8, 40.7)
Missing	41		1003	
Very severe CP^c	168	36.1 (31.9, 40.2)	1943	22.3 (21.4, 23.1)
Missing	30		562	
Visual impairment	270	55.3 (51.0, 59.6)	4372	45.9 (44.9, 46.9)
Missing	40		617	
Hearing impairment	39	8.5 (5.9, 11.1)	728	8.0 (7.5, 8.6)
Missing	47		805	
Epilepsy	343	66.9 (62.9, 71.0)	3472	36.1 (35.1, 37.0)
Missing	22		587	
Severe speech disorder^d	125	50.1 (44.0, 56.2)	1464	34.3 (32.9, 35.7)
Missing	40		938	
Postneonatal imaging performed^{d,e}	263	92.3	4131	79.6
MRICS results^{d,e}				
Maldevelopment	2	0.8 (0.2, 3.3)	448	11.9 (10.9, 13.0)
Predominant white matter injury	21	8.6 (5.7, 12.9)	1947	51.9 (50.3, 53.5)

(Continues)

TABLE 3 | (Continued)

	Total postneonatal CP		Total pre/peri/neonatal CP	
	N = 533		N = 10,219	
	n	% (95% CI)	n	% (95% CI)
Predominant grey matter injury	135	55.6 (49.2, 61.7)	692	18.4 (17.2, 19.7)
Miscellaneous	80	32.9 (27.3, 39.1)	367	9.8 (8.9, 10.8)
Normal	5	2.1 (0.9, 4.9)	300	8.0 (7.2, 8.9)
Missing	20		377	

^aFrom 2009 onwards only.

^bSevere CP: GMFCS IV–V or IQ < 50.

^cVery severe CP: GMFCS IV–V and IQ < 50.

^dFrom 2007 onwards only.

^eNo imputation for postneonatal imaging data and results.

been described almost constantly [4, 6, 7], including for much earlier generations [24]. In our data, infectious events were the category with the highest proportion of preterm births. This could suggest a pre-existing fragility due to preterm birth, making these children particularly vulnerable to the risk of serious postnatal infection such as previously reported [25, 26] that could result in brain damage, whether directly or by an indirect mechanism.

Comparisons between PPNC and PNCP revealed that unilateral forms were predominant in PNCP (44.1%). Cerebral palsy was more severe in the PNCP group, in terms of both motor and intellectual limitations, and associated epilepsy or language disorders were also significantly more frequent. Overall, we reported higher proportions of associated impairments than that reported by the Australian network [4], although the severity thresholds were not identical. Lastly, we reported very different imaging patterns between the PNCP and PNNCP groups. These patterns, which had never been described in this way in the literature, reflected the different origins and timing of brain injury between these two groups. In the PNCP group, grey matter lesions predominated and white matter lesions represented less than 10%.

Analysis of the clinical characteristics of PNCP according to the events at the origin of injury showed differences in type and severity of CP. Overall, PNCP with a primary event classified as D-CVA presented the least severe motor impairment and the lowest proportion of associated disabilities (except epilepsy). Recent ACPR data showed similar findings [4]. Although very rare, PNCP with primary events classified as E-Hypoxic showed the most severe forms of impairment (motor and intellectual) and the highest proportion of speech disorders. A higher proportion of deafness was observed for infectious causes (consistent with meningitis or encephalitis) and a higher proportion of visual impairment for head trauma. This is consistent with the mechanisms involved in the onset of injury. Lastly, our findings confirmed that cardiac malformations were more frequent in PNCP than in PPNC [27]. These malformations were clearly linked to events at the origin of the brain lesion, whether surgery-related (category C) or CVA (category D).

6 | Conclusions

This study confirmed the decline in the prevalence of PNCP in Europe, particularly PNCP due to infectious causes, although these remain the most common. This suggests that while the results of preventive measures for infectious causes seem encouraging, preventive measures for other causes of PNCP should be pursued, adapted and amplified. Prevention efforts, including for infectious causes, should be maintained among children born prematurely, who are particularly at risk of developing CP in the postneonatal period. Children with PNCP are generally more severely impaired than those with PPNC, with differences in severity depending on the primary event involved. Better understanding of the disorders associated with CP for each of the causes underlying brain injury would help to improve management and prevention and to better assess the prognosis for each cause.

Author Contributions

M. Delobel-Ayoub was involved in developing the classification and in reviewing all the PNCP cases, designing the study, collecting the data, carrying out statistical analysis, interpreting the data, writing the first drafts of the article and reviewed the drafts. V. Ehlinger was involved in the conception of the study, carrying out statistical analysis and interpreting the data, she participated in writing the first drafts and reviewed the drafts of the article. D. Klapouszczak, A. Troha Gergeli, E. Sellier, K. Hollody, D. Virella, T. Vik and K. Horridge, were involved in collecting the data, they participated in the development of the classification, participated in reviewing all the PNCP cases to ensure standardised classification of the primary event, participated in the interpretation of the data and reviewed the drafts. N. Vidart d'Egur-bide Bagazgoitia and C. Perret participated in the interpretation of the statistical analysis and results and reviewed the drafts. C. Arnaud coordinated the working group and coordinated the study, participated to data analysis and interpretation of data and results and reviewed the drafts.

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Ethics Statement

This study was based exclusively on pseudonymised registry data compiled at European level in the SCPE database. It did not require any contact with the registered persons. Therefore, ethical review and approval were not required for this study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

Social Media Quote

The prevalence of postneonatal cerebral palsy decreased in the SCPE network, particularly for infectious causes which remain the most frequent. PNCP cases were more severe and brain imaging patterns differed from pre/perinatal CP. PNCP severity differed according to cause.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.