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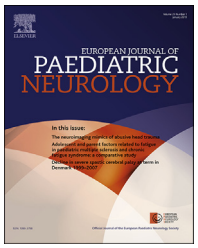

Original article

Decline in severe spastic cerebral palsy at term in Denmark 1999–2007

Christina Engel Hoei-Hansen [a,*], *Bjarne Laursen* [b], *Jens Langhoff-Roos* [c], *Gija Rackauskaite* [d], *Peter Uldall* [a]

[a] *Department of Paediatrics, Copenhagen University Hospital, Rigshospitalet, Denmark*
[b] *National Institute of Public Health University of Southern Denmark, Denmark*
[c] *Department of Obstetrics and Gynecology, Copenhagen University Hospital, Rigshospitalet, Denmark*
[d] *Department of Paediatrics, Skejby University Hospital, Aarhus, Denmark*

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ABSTRACT

Aim: To analyse trends in prevalence and severity of cerebral palsy (CP) in Denmark in birth years 1999–2007 and compare with previous periods.
Method: Data has been collected uniformly in the Danish cerebral palsy national register nationwide since 1995. Rates in the time periods 1999–2001, 2002–2004 and 2005–2007 covering 585,393 births were analysed by gestational age and subtypes.
Results: Total number of CP cases in the period was 1165. The overall prevalence of CP decreased significantly from 2.1 in 1999–2001 to 1.8 in 2005–2007 per 1000 livebirths ($p = 0.022$). The decline was only significant for children born at term ($p = 0.007$) but not for the preterm ($p = 0.44$). The decline in children born at term was based on a decrease in bilateral spastic CP ($n = 117$ in years 1999–2001 and $n = 59$ in 2005–2007). Multidisciplinary obstetric skills training with neonatal resuscitation in Denmark was initiated in 2003 and timely associated with the decrease. The prevalence of unilateral spastic CP the prevalence did not change, but in the two last time periods more children had a right-sided than left-sided unilateral spastic CP.
Conclusion: The decline in rate of CP seen in 2005–2007 as compared to 1999–2001 was mainly based on fewer cases of severe spastic CP in term infants. We hypothesize that improved neonatal resuscitation in the delivery room may be partly responsible for the decrease. In premature children the decline was not significant in this time period, but has been dramatically decreasing in the years before the time period here analysed.

Abbreviations: CI, confidence interval; CP, cerebral palsy; CT, computed tomography; DQ, developmental quotient; GA, gestational age; GMFCS, gross motor function classification system; MRI, magnetic resonance imaging; SCPE, Surveillance of Cerebral Palsy in Europe; SD, standard deviation.

* *Corresponding author*. Department of Paediatrics, Copenhagen University Hospital Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø Denmark.
E-mail address: chh@dadlnet.dk (C.E. Hoei-Hansen).

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1. Introduction

The Danish Cerebral Palsy Registry (DCPR) is one of the largest single-nation cerebral palsy (CP) registers and has existed since 1967.[2] Initially it covered only Eastern Denmark (about 50% of the population) but from birth year 1995 and onwards it is a national registry. Data is shared with the Surveillance of Cerebral Palsy in Europe, SCPE.[18]

CP is the most common cause of childhood-onset, lifelong physical disability with a range of implications for the patients and health social services.[3] The diagnosis of CP covers an array of underlying diagnoses and conditions. By definition CP is a group of permanent but not unchanging disorders of movement and/or posture and of motor function, which are due to a non-progressive interference, lesion, or abnormality of the developing/immature brain.[16,18] Prevalence of CP increased in the 1970s but has been lower thereafter. In the study by Hirvonen et al. covering years 1991–2008 in Finland the decrease in CP was found to be non-linear, with the highest risk in the group of very preterm children and lowest after year 2001.[6] Another study covering recent years showed a non-significant decrease in Japan in years 2001–2010.[8] In data from the Australian CP register covering years 1993–2006 overall CP rates were unchanged,[13,17] whilst the European multi-center study by Sellier et al. showed a mean annual fall of 0.7% from years 1980–2003.[15] Several classification types have been applied covering the wide spectrum of motor disability often accompanied by cognitive deficits, visual impairment or epilepsy.[19]

We report nationwide data according to gestational age, severity and subtypes of CP in the period 1999–2007 and owing to a systematic data collection are able to compare data back to 1983.

2. Materials and methods

The standardised data sampling of the Danish CP cases has been described previously.[12] The full case reports are obtained and the diagnosis is evaluated by four trained neuropaediatricians before inclusion when the child is 5–6 years old. A data abstraction form (specific information on pregnancy, birth, neonatal period, impairments and demographic data) is filled in for every included child. Supplementary demographic and obstetric data are collected from the Danish Medical Birth Registry. A validation of the registry has been performed.[20] Inclusion criteria for the CP register are: 1) Born in Denmark and still living at age 4–5 years. If the child dies between age 1 and 4–5 years, it is included anyway provided the CP-diagnosis is unquestionable, 2) Pre- or perinatal aetiology (before 28th day of life), 3) Fulfilment of diagnostic criteria according to SCPE.[18]

Parameters used to characterise the degree of handicap were estimated developmental quotient (DQ), motor function and presence of epilepsy after the neonatal period. The DQ, which is based on assessment from the medical records, is divided into 1) normal for children without learning disabilities and expected to start normal school (IQ above 85), 2) abnormal for children with moderate learning disabilities and need of special education/attendance of special schools and 3) children with a severe mental handicap (IQ below 50). Motor function was based on the gross motor function classification system (GMFCS) level at data extraction time. Data on number of live births used as the denominator was obtained from The Danish Birth Register. When testing for trend the Cochran–Armitage test for trend was used. The level of significance was set at 0.05.

3. Results

For birth years 1999–2007 1165 CP cases were registered, corresponding to a total prevalence of 1.99 per 1000 live births (95% CI 1.88–2.11). Among children with CP 59.7% were boys. Among the patients with known gestational age (n = 1150) 684 children were born at term (37–41 weeks; 59.5%). Of those born preterm, 67 were born extremely preterm (<28 weeks; 5.8% of all CP cases), 177 very preterm (28–31 weeks; 15.4%) and 198 were moderate to late preterm (32–36 weeks; 17.2%). Total births in Denmark was 585,393 in 1999–2007, of whom 38,969 (6.7%) were born preterm.

The overall prevalence declined from 2.1 in 1999–2001 to 1.8 per 1000 live births in 2005–2007 ($p = 0.022$, Table 1). The decline was only significant for children born at term, not for the preterm ($p = 0.007$ and $p = 0.44$, respectively). As is

Table 1 – Prevalence of CP per 1000 live births in the total population, and spastic unilateral and bilateral CP in children born at term (≥37 weeks) and preterm (<37 weeks).

	1999–2001			2002–2004			2005–2007		
	No. cases	No. liveborn	Prevalence	No. cases	No. liveborn	Prevalence	No. cases	No. liveborn	Prevalence
Total*	415	198,762	2.1	369	193,283	1.9	342	193,348	1.8
Preterm	153	12,619	12.1	144	13,282	10.8	145	13,068	11.1
Term*	262	186,143	1.4	225	180,001	1.2	197	180,280	1.1
Unilateral spastic	159	198,762	0.8	147	193,283	0.8	162	193,348	0.8
Preterm	54	12,619	4.3	48	13,282	3.6	49	13,068	3.7
Term	100	186,143	0.5	91	180,001	0.5	106	180,280	0.6
Bilateral spastic	211	198,762	1.1	181	193,283	0.9	150	193,348	0.8
Preterm	90	12,619	7.1	81	13,282	6.1	85	13,068	6.5
Term	117	186,143	0.6	95	180,001	0.5	59	180,280	0.3

*= $p < 0.05$ for trend. Total numbers are not equal to preterm + term as GA is not known for all spastic patients.

depicted in Fig. 1A, the decline for preterm children was considerably larger in the period from 1983 to 1998.

For the unilateral spastic CP the incidence remained unchanged in total (Fig. 1B; p = 0.74), both for children born at term (p = 0.51) and preterm (p = 0.54; Fig. 2A). The proportion of all CP cases being unilateral right-sided increased in the time-period, as 19.6% of all cases were unilateral right in the birth years 1999–2001 as compared to 29.7% in 2005–2007 (p = 0.025; Table 2).

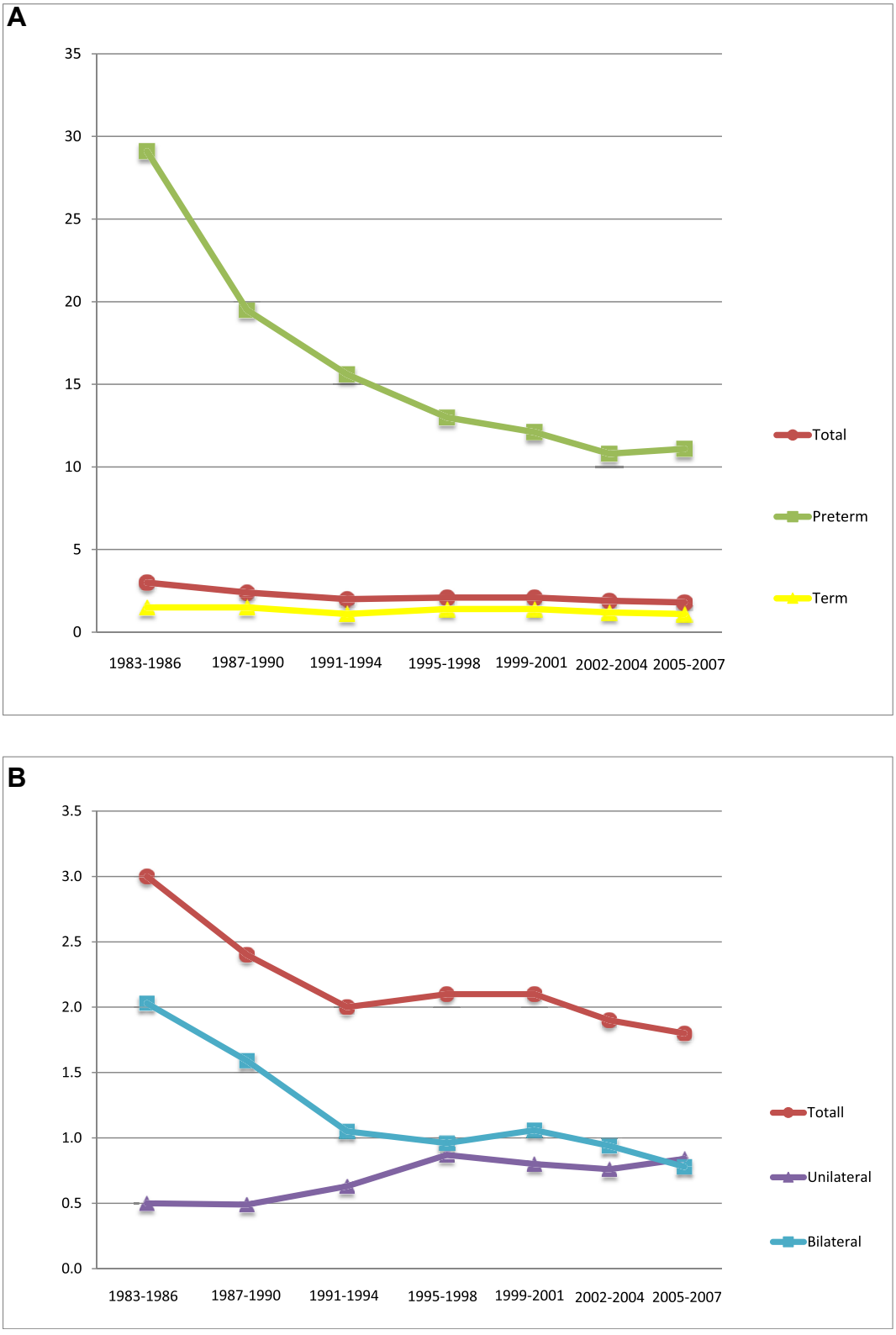

Fig. 1 – Prevalence of CP per 1000 live births according to A) gestational age and B) CP type. Data years 1983–1998 are from Ravn et al.[12] and are only based on Eastern Denmark.

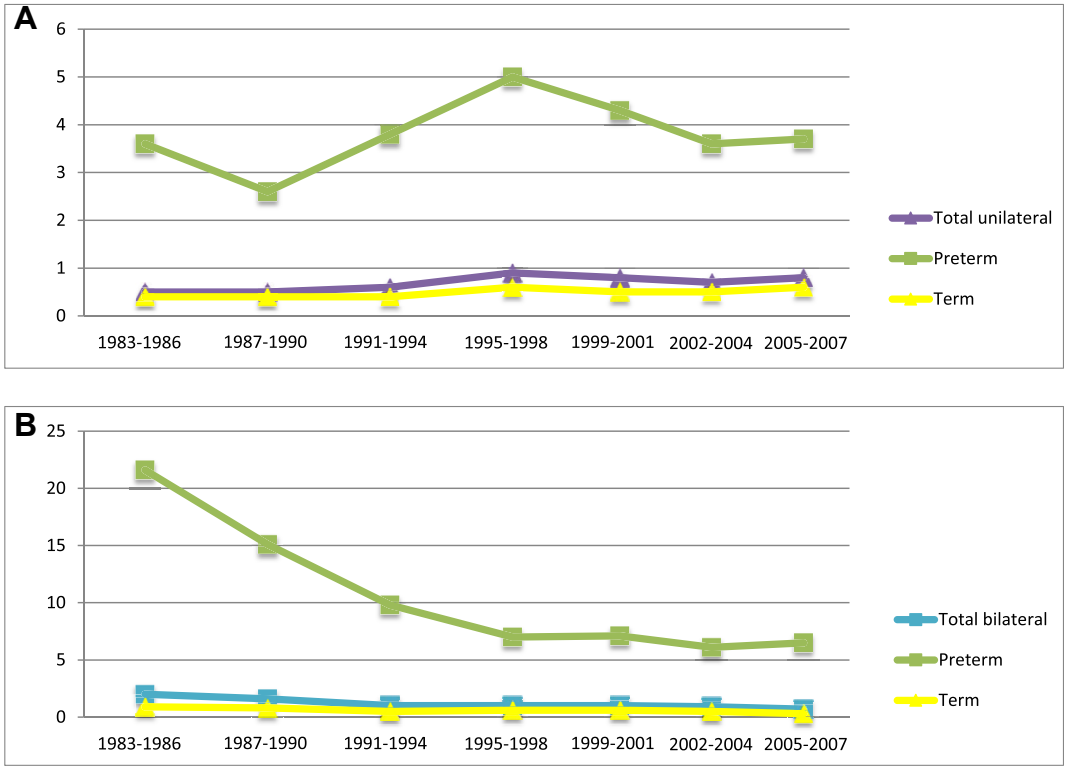

Fig. 2 – Prevalence per 1000 live births of A) unilateral and B) bilateral spastic according to gestational age. Data years 1983–1998 are from Ravn et al.[12] and are only based on Eastern Denmark.

For bilateral spastic CP the incidence declined in total from 1.0 to 0.7 per 1000 live births ($p = 0.002$; Table 1). The decline was statistically significant for children born at term ($p < 0.0001$), but not for children born preterm ($p = 0.54$; Table 1). The proportion of the severely affected cases (GMFCS level III–V) remained stable at approximately 63% of the preterm bilateral spastic CP cases (Table 2). For the children born at term there were slightly more severely affected cases (68.4% in 1999–2001 and vs. 73.9% in 2005–2007).

The number of children with dyskinetic and ataxic CP remained stable in the three time periods (Table 2). Dyskinetic CP was seen in 102 (8.8% of all CP cases), of whom 78 were born at term. There were 37 children with ataxic CP (3.2%), of whom 26 were born at term.

The GMFCS level among all cases was distributed as follows: 44.3% were GMFCS level I, 13.3% were level II, 5.7% were level III, 15.6% were level IV and 21.0% were level V (missing data in 17). DQ was estimated as normal in 45.6%, judged as IQ level 50–85 in 27.5% and below 50 in 26.9% (missing data in 122). Epilepsy was seen in 32.3% at some point after the neonatal period, and 25.2% were at age 4–5 years still treated with an anti-epileptic drug.

The number of CP cases born postterm (≥ gestational week 42) decreased in the period, as there were 37 in 1999–2001, 32 in 2002–2004 and 20 in 2005–07. The antepartum, peripartum, and neonatal risk factors and outcomes among children born preterm or at term are depicted in Table 3. For the preterm CP cases there was a significant reduction in maternal morbidity (preeclampsia and other disorders) and in mothers receiving antenatal corticosteroid. There were significantly fewer CP cases that in the neonatal period had been in need of treatment for hyperbilirubinaemia and who had sepsis, but an increasing proportion that had an abdominal complication. Among the term CP cases none of the analysed prenatal risk factors changed significantly and among the analysed perinatal risk factors there was only a significant reduction number of cases with sepsis.

4. Discussion

In this current report on the latest 1165 registered cases of CP in Denmark, we find a slight decrease in overall prevalence of CP. The overall prevalence in the time period 1999–2007 is 1.99 per 1000 live births. Within the 9-year period described, the overall prevalence of CP decreases slightly, but significantly from 2.1 in 1999–2001 to 1.8 in 2005–2007 per 1000 live births ($p = 0.022$). This fall is dramatically different as compared to former time periods, where the prevalence was 3.0 per 1000 live births in 1983–1986.[12]

Total prevalence of bilateral spastic cases in 1999–2007 decreased due to a significantly lower prevalence in children born at term. In premature children the decline was not significant in this time period, but has been dramatically decreasing in the years before the time period here analysed. We find significant changes in the children born preterm

Table 2 – Distribution of CP type. Cases are divided according to gestational age (preterm <37 weeks and term ≥37 weeks). Cases were only included if CP type was known.

Preterm % (numbers)	1999–2001 (152)		2002–2004 (142)		2005–2007 (total 144)	
Bilateral spastic	59.2%	(90)[b]	57.0%	(81)[b]	59.0%	(85)[b]
Bilateral mild	37.0%	(33)	36.3%	(29)	36.5%	(31)
GMFCS I + II	(GMFCS I = 25, II = 8)		(GMFCS I = 17, II = 12)		(GMFCS I = 13, II = 18)	
Bilateral severe	62.9%	(56)	63.8%	(51)	63.5%	(54)
GMFCS III + IV + V	(GMFCS III = 1, IV = 31, V = 24)		(GMFCS III = 7, IV = 29, V = 15)		(GMFCS III = 18, IV = 23, V = 13)	
Unilateral spastic	35.5%	(54)	33.8%	(48)	34.0%	(49)
Unilateral right	46.3%	(25)	62.5%	(30)	63.3%	(31)
Unilateral left	53.7%	(29)	37.5%	(18)	36.7%	(18)
Dyskinetic	3.2%	(5)	6.3%	(9)	4.9%	(7)
Ataxic	2.0%	(3)	2.8%	(4)	2.1%	(3)
Term % (numbers)	**1999–2001 (total 257)**		**2002–2004 (total 222)**		**2005–2007 (total 193)**	
Bilateral spastic[a]	45.5%	(117)	42.8%	(95)	30.6%	(59)[b]
Bilateral mild	31.6%	(37)	32.6%	(31)	26.3%	(15)
GMFCS I + II	(GMFCS I = 29, II = 8)		(GMFCS I = 22, II = 9)		(GMFCS I = 5, II = 10)	
Bilateral severe	68.4%	(80)	67.4%	(64)	73.7%	(42)
GMFCS III + IV + V	(GMFCS III = 5, IV = 25, V = 50)		(GMFCS III = 6, IV = 19, V = 39)		(GMFCS III = 6, IV = 10, V = 26)	
Unilateral spastic	38.9%	(100)	41.0%	(91)	54.9%	(106)
Unilateral right	55.0%	(55)	59.3%	(54)	65.1%	(69)
Unilateral left	45.0%	(45)	40.7%	(37)	34.9%	(37)
Dyskinetic	11.2%	(29)	11.8%	(26)	11.9%	(23)
Ataxic	4.3%	(11)	4.5%	(10)	2.6%	(5)
Preterm + term	**1999–2001 (n = 409)**		**2002–2004 (n = 364)**		**2005–2007 (n = 337)**	
Unilateral right[a]	19.6%	(80)	23.1%	(84)	29.7%	(100)
Unilateral left	18.1%	(74)	15.1%	(55)	16.3%	(55)

Abbreviations: GMFCS = gross motor function classification system.
[a] $p < 0.05$ for trend.
[b] some with unknown GMFCS status.

related to prenatal care (less mothers with preeclampsia, maternal disorder and less treatment with corticosteroid) and in the perinatal care (less children with hyperbilirubinaemia, sepsis and abdominal complications). These changes were associated with a sustained low, but not decreasing, CP prevalence. Improvements in some areas of perinatal care in preterm born infants may have been counterbalanced by deterioration in others leading to our finding of no overall improvement. Which factors these may be are not evident from our study. We find a low and decreasing number of children, which are treated with antenatal corticosteroid. The low rate of corticosteroid treatment may be due to incomplete registration, as the data is based on information given in patient records. Nevertheless a decrease is also seen in presence of maternal preeclampsia and may reflect a change in perinatal care. Steroid in case of assumed imminent preterm delivery before 34 weeks of gestation is given when time allows. We do not have data on steroid use in the background population of preterm deliveries without CP in our population.

In the population of children born at term there were no significant changes in prenatal factors, but there were significantly less children with neonatal sepsis (a reduction from 24.9% to 15.0%). The occurrence of CP in the preterm and term population may reflect different causal mechanisms. We can only speculate in order to provide a cause to the decline in prevalence of children born at term with CP. That the detected lower proportion of cases having sepsis should alone be the explanation for the declining prevalence seems less probable, but less sepsis cases may be one cause. The decline in the CP of term infants may be due to several factors, of which some may not have been incorporated in the registration. Several gradual changes have been implemented in obstetric care during the time period. It is interesting that we find fewer postterm CP cases coinciding with an increase in induction of labour in late pregnancy,[4] even though the major change in policy occurred after the investigated time period.

Falling CP prevalence may reflect changes in obstetric and neonatal care among cases caused by hypoxia during labour or a critical illness in the neonatal period. In the time period investigated, obstetric routines have gradually changed. Ultrasonography in pregnancy was used with more sensitive cut off values for foetal growth for improved prediction of intrauterine growth retardation, induction of labour at term increased and foetal surveillance during labour at term increasingly used cardiotography with ST-analysis. These changes might have had an impact on cerebral palsy subtypes and rates. Studies on obstetric skills training has shown an increase in knowledge and skills of the subjects taught, but in general, studies have failed to document a significant improvement in clinical outcomes. In 2003, the first national courses on obstetric skills training (ALSO) started in Denmark, and in 2008 nearly all obstetric units had local training.[10]

Table 3 – Prenatal, perinatal and outcome characteristics of preterm and term children with CP in Denmark in 1999–2007.

	Preterm[a]				Term[b]			
	1999–2001	2002–2004	2005–2007	p	1999–2001	2002–2004	2005–2007	p
Prenatal factors								
Gender male	52.9	65.3	59.3	.27	62.8	57.5	61.0	.71
Preeclampsia	14.4	11.9	6.5	.031	5.7	2.5	3.0	.22
Maternal disorder (chronic disease, drug use or retardation)	19.1	13.3	6.5	.002	9.8	5.5	5.8	.15
Antenatal corticosteroid	12.9	5.9	5.1	.021	6.0	2.0	6.0	.99
Multiple birth	27.6	32.6	35.9	.13	4.3	3.9	5.6	.52
Congenital malformation outside CNS	7.3	5.7	9.9	.43	15.6	16.3	13.8	.61
Perinatal factors								
Fever during labour	8.2	3.8	5.1	.30	2.2	2.0	1.2	.70
Caesarean section	61.6	60.0	52.9	.13	29.6	31.2	31.3	.71
Apgar at 5 min below 7	8.8	11.6	6.4	.45	20.8	19.7	16.1	.23
Surfactant treatment	27.3	28.6	24.8	.63	0	1.0	1.2	.17
Anaemia treated with transfusion	21.6	20.5	14.0	.093	2.1	5.9	4.2	.24
Hyperbilirubinaemia, treated	73.8	72.4	54.8	.001	6.5	2.5	4.2	.34
Sepsis	58.1	54.4	46.0	.041	24.9	21.3	15.0	.016
Neonatal seizures	12.0	11.7	5.8	.064	32.5	28.9	25.3	.12
Cardiac disease in neonatal period	11.2	5.1	12.1	.82	3.0	1.5	3.5	.77
Abdominal complication in neonatal period	6.6	8.0	15.1	.019	1.7	0.5	0.6	.40
Neonatal cerebral irritation or depression	28.4	27.9	25.0	.52	39.7	36.1	33.9	.23
Cerebral infection in neonatal period	1.3	3.6	2.2	.67	2.1	2.0	1.2	.70
Outcome features								
GMFCS III, IV or V	44.7	43.7	42.4	.68	44.8	43.6	36.8	.11
Epilepsy ever	22.9	26.1	28.6	.22	33.3	33.0	48.0	.003
Epilepsy treated at age 4–5 y	17.2	20.0	23.7	.17	26.7	25.6	40.2	.005
Visual impairment	17.8	13.7	16.9	.84	20.8	20.5	20.0	.85
DQ normal	47.6	52.6	46.5		42.9	43.6	45.7	
DQ 50–85	32.9	30.8	31.9	.091	23.8	23.1	26.9	.43
DQ < 50	19.5	16.5	21.5		33.3	33.3	27.4	

[a] Preterm – GA<37 weeks (n = 442).
[b] Term – GA 37–41 weeks (n = 684).
GA was unknown for 15 children. Children with GA ≥ 42 weeks are not included (n = 24). p = statistic significance between proportions or medians in the three time periods.

Midwives and obstetricians who attended these courses received both theoretical and – probably more important – practical skills training in neonatal resuscitation of infants with unexpected asphyxia at term. The focus on immediate and appropriate treatment of these infants should lead to less severe neonatal asphyxia, and might explain the less severe CP (significant decrease of bilateral vs. total spastic CP) in term neonates in the last period of our study. Future detailed follow-up of the next three-year period will reveal if this change in the CP pattern is stable and hopefully find that the focused education of staff is worthwhile measured by long-term outcomes such as severe spastic CP.

Thus, the register data supports the idea that improved perinatal care may reduce the proportion of children with birth hypoxia, neonatal seizures, infection and cerebral affection among term children with CP during the time period (Table 3). Cooling of asphyxiated infants with severe neonatal asphyxia was introduced in Denmark after 2007, and will hopefully reduce the number of cases with severe GMFCS in the future.

Necrotising enterocolitis is a risk factor of CP,[14] and an increased proportion of preterm CP children had this abdominal complication during the time period (6.5–15.1%), which could be part of the stable levels of cases among the premature children. In our cohort there was an increased proportion of children with epilepsy, increasing among the children born at term from 33.3% in 1999–2001 compared to 48.0% in 2005–2007. This may reflect variations in diagnosis or may indicate a changing pattern of pathogenesis and needs further exploration of patterns of cerebral MRI in children with CP during this period. The cognitive outcome has only shown an insignificant improvement and remained unchanged in this time period. The proportion with visual impairment likewise remained unchanged.

Total incidence of the unilateral spastic CP is unchanged, but there has been a significant increase in right-sided as compared to left-sided cases in recent years. This may reflect changes in the aetiological patterns in CP with increasing proportion of arterial stroke, which are known to preferably affect the left hemisphere.[7] At the moment, the knowledge about differences in aetiology is sparse, as the one study with 60 children with unilateral CP revealed no differences in perinatal risk factors in 2004.[9] In order to investigate this assumption about increasing role of arterial unilateral stroke, further studies should include both perinatal risk factors and MRI findings.

The classification of cerebral palsy has changed slightly over the years and the more precise definition introduced may have introduced information bias and be partly responsible

for the reported reduction in prevalence of CP in recent years. Although the register has been validated in 1997, there could have been an influence on diagnosis. During the last six birth year periods the definition has however been unchanged. Another potential limitation of the study is the risk that the neuropediatricians extracting information from the case notes may not have followed the definitions uniformly. Strengths of the study include the detailed available information on prenatal, perinatal and neonatal care due to systematic data collection. The Danish CP register is comprehensive and population-based and cover a very significant number of children. The national health register in Denmark is well established and diagnoses can be considered reliable. CP diagnoses are only made in neuropaediatric units of public hospitals, but since a CP diagnosis is necessary for obtaining physiotherapy free of charge in Denmark, the risk of missing CP cases is low, but not all cases in the national health register fulfil SCPE criteria, and at data extraction from the national health register to the CP register up to half of the national health register cases are excluded.

Study design of CP registration can be performed very diversely.[17] Nevertheless recent publications from other regions report an overall prevalence of CP at similar levels. In western Sweden the prevalence in 2003–2006 was 2.18 per 1000 live births[5] and in a Finnish national registry CP incidence was found to be 0.22% in years 1991–2008 with a non-linear decrease over time.[6] In Australia an overall CP prevalence based on registry data from some regions was 2.1 per 1000 live births in years 1993–2006.[17] In a Japanese region CP prevalence, excluding congenital anomalies, was 1.5 per 1000 in 2001–2001 and 1.3 per 1000 in 2006–2010.[8] Our data from earlier time periods have been included in a large European SCPE registry covering 20 population-based registries, in which a decline was seen from 1.90 per 1000 live births in 1980 to 1.77 in 2003.[15] And an American study of 8-year old children found a declining prevalence from 3.5 per 1000 in 2006 to 2.9 per 1000 in 2010.[1] However, the timely trends in the prevalence of CP – in our as well as other studies - may reflect some gradual changes in diagnostic thresholds, variation of recognition of CP or cohort effect.

Compared to previous studies a new finding is the decline in prevalence among children born at term. The present study of CP infants born in years 1999–2007 have implications for public health monitoring by documenting the progress made in perinatal care at term by reducing the number of CP cases in Denmark.

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Conflicts of interest

The authors have no potential conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejpn.2018.08.010.

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