Open access • Journal Article • DOI:10.1007/S10654-010-9474-0

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Published on: 08 Jun 2010 - European Journal of Epidemiology (Springer Netherlands)

Topics: Cerebral palsy, Population, Spastic and Prevalence

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Trends in Prevalence of Cerebral Palsy in Children born ≥ 2500g in Europe from 1980 to 1998.

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ABSTRACT

Time trends for cerebral palsy (CP) prevalence in children born ≥ 2500 g vary across studies and scarce data exist on trends by subtype of CP. The objective of this study was to describe changes in prevalence of CP in infants born ≥ 2500 g between 1980 and 1998 in Europe. Data were collated from the SCPE (Surveillance of Cerebral Palsy in Europe collaboration) common database. Poisson regression was used to test for change in prevalence over time. Birth year and register effects were explored and trends in prevalence were estimated by CP subtype and severity. Four thousand and two children with CP and birthweight ≥ 2500 g were recorded in 15 population based-registers. The overall prevalence of CP was 1.16 per 1000 live births (0.88−1.48) in 1980 and 0.99 (CI, 0.80−1.20) in 1998. The trend was not significant (*P*=.14), except in two registers. However, there were significant changes in the prevalence of spastic CP subtypes, with a decrease in the bilateral spastic form (*P* <.001), and an increase in the unilateral spastic form (*P*=.004). There was a concurrent reduction in neonatal mortality from 1.7 (CI, 1.4−2.1) to 0.9 (CI, 0.7−1.1) per 1000 live births with birthweight ≥ 2500 g. In conclusion, for children born with birthweight ≥ 2500 g, the prevalence of CP in Europe was stable in spite of changes by subtype and a significant decrease in neonatal mortality.

Keywords: Cerebral palsy, Children with birthweight ≥ 2500 g, Europe, Prevalence, Statistical interaction.

INTRODUCTION

Cerebral palsy (CP) is the most common cause of significant motor impairment in children. Approximately 2 children in every 1000 born alive suffer from CP. Although the risk of having CP is greatly increased for those born very preterm or with very low birthweight,[1] children with birthweight ≥ 2500 g, what we shall call normal birthweight (NBW) for the purpose of this paper still account for most children affected. More than half of the children born during the 1970s and 1980s with CP and recorded on a European database, weighed more than 2500 g at birth;[2] the situation is similar in the USA[3], Australia [4] or China. [5]

Less research has been carried out on the epidemiology of CP in children of NBW than in those of very low birthweight (< 1500 g). As the number and severity of impairments increase with increasing gestational age [6, 7] and birthweight,[8] the type of brain lesion among term or NBW children tends to exhibit a different pattern to that of preterm or low birthweight births.[9-11] Time trends for CP prevalence in NBW children vary across studies.[12, 13] Most of them reported stable prevalence rates from the 1970s to the 1990s. [4, 14-17] However, a small increase was reported in USA between 1975 and 1991 [18] while in Sweden the monitoring from the 1950s to the 1990s showed an increase in prevalence from the beginning of the 1970s to the mid 1980s followed by a decrease. [19] Also, in Iceland a decrease in prevalence for term babies was observed in 1997-2003 in comparison with 1990-1996. [20]

In 1998, a network of population-based CP registers, Surveillance of Cerebral Palsy in Europe (SCPE),[21] was established. It is the largest international collaboration of CP

registers in the world. Anonymous data, now covering 19 registers, are held in the common database. Data are recorded and coded according to agreed definitions.[22]

This paper aims to establish whether the prevalence of CP in NBW children altered in Europe between 1980 and 1998 using multicentre analysis methods. Reporting of secular trends for main neurologic subtypes and severity of impairment were also made possible as a result of the large database available.

MATERIAL AND METHODS

Definition and classification

All registers contributing to the network are population-based, covering either a region or a whole country. Data were collated from SCPE common database as described previously.[2, 21] CP is defined as a group of permanent, but not unchanging, disorders of movement and/or posture and of motor function, due to a non-progressive interference, lesion, or abnormality of the developing/immature brain. Progressive motor disorders, nerve or muscular diseases and brain metabolic disorders are excluded. The diagnosis of CP is confirmed at around age 5 years, before submission by each register of its data to the SCPE common database. Subtypes of CP are defined as unilateral spastic, bilateral spastic, dyskinetic or ataxic. Hierarchic trees developed by SCPE were used to implement inclusion and exclusion criteria and classify CP subtypes consistently among registers. [2, 21]

Study population

Children with CP born from 1980 to 1998, whose mothers lived in an area covered by a contributing register at birth, were eligible for this study. We selected children with birthweight ≥ 2500 g. Post-neonatal CP cases were excluded. Annual population data for live births, stratified by birthweight were provided by each register except four, for which these data were not available by birthweight (SCPE_C02 in Toulouse, France; SCPE_C07 in Dublin, Ireland; SCPE_C14 in Arnhem, Netherlands and SCPE_C21 in Lisbon, Portugal). Data from these four registers were consequently excluded from analysis. One register, SCPE_C10 in Tübingen, Germany, recorded only bilateral spastic CP cases and its data were included only when analyzing the bilateral spastic subgroup. The SCPE_C01 register in

Grenoble, France, has specific migration patterns and cases were defined as living in the area at the time of registration.

Characteristics of the children

Classification of CP subtypes followed SCPE classification.[22],[23] Severe intellectual impairment was defined as IQ below 50; epilepsy as a history of two unprovoked seizures before confirmation of CP diagnosis, excluding febrile or neonatal seizures; severe visual impairment as visual acuity of < 6/60 (Snellen scale) or 0.1 (Decimal scale) in the better eye following correction and severe hearing impairment as a loss of > 70 dB in the better ear before correction. Severity of CP was assigned to three categories.[24] Severe CP was defined as children with IQ < 50 and unable to walk, even with assistive devices. Moderate CP was defined as children with IQ < 50 and able to walk; or children with IQ ≥ 50 and unable to walk without assistive devices. Mild CP was defined as children with IQ ≥ 50 and able to walk without assistive devices. To analyze trends in prevalence, we combined moderate and severe CP into a moderate-to-severe group. A Z-score for birthweight by gestational age was derived for each child. For Swedish children, Marsal fetal growth standard curves were used; [25] Gardosi fetal growth standard curves were used for children of all other registers. [26]

Statistical methods

We report descriptive statistics as percentages or as mean with standard deviation (SD). To study changes in characteristics of children with CP over time, we considered 4 periods: 1980-1984; 1985-1989; 1990-1994, and 1995-1998, and we adjusted on register effect to take account of the fact that the number of registers contributing data differed between the periods. Binary variables were analyzed using the Chi-square test for trend

adjusting on register, provided that the Chi-square test for non-linearity was not significant. Continuous variables were analyzed using linear regression analyses adjusted for period and register.

Poisson regression was used to investigate trends in prevalence of CP. Given that data were provided by different registers covering varying periods, we followed several steps. Firstly, we analyzed trends in prevalence within each register with a linear term for individual birth year. We tested non-linearity of the trend using polynomial terms for birth years up to third order. Secondly, we used pooled data to investigate trends in Europe. The initial model contained just individual birth years. Addition of a term for register allowed testing for a register effect. Then, adding an interaction term between register and birth year provided a test for variation in trends between registers. We also tested non-linearity of the trend using polynomial terms for birth years up to third order. Likelihood-ratio Chi squared tests were used to compare nested models. The same modeling strategy was used when analyzing time trends by CP subtype and by severity.

To assess the robustness of our results, we performed cross-validation by sequentially removing each register from the model. We verified that the registers responsible for interaction were also those responsible for the main changes in the prevalence estimates when removed sequentially from analysis.

In order to minimize findings that were of statistical significance but little clinical relevance in such a large dataset, the threshold selected for overall analyses was $P<.005$. The threshold for analyses of individual registers data was $P<.05$. We present prevalence rates with Poisson 99% confidence intervals for pooled data and with 95% confidence intervals for individual

registers. Statistical analyses were performed using Stata Statistical software (version 10.0, Stata Corp., College Station, TX, USA).

RESULTS

Characteristics of the children with cerebral palsy included in the study

Fifteen SCPE registers provided data on 7507 children with known birthweight from 1980-1998. Of those, 4002 (53%) were born with birthweight ≥ 2500g and were included in the study (Figure 1). The type of CP was spastic in 84.9% of cases (bilateral in 45.7%, unilateral in 39.2%), dyskinetic in 9.3%, and ataxic in 5.8% (Table 1). Among these children 2290 (58.0%) were male, 3520 (91.2%) were ≥ 37 weeks gestational age, and 3772 (97.4%) were singletons. Of 2518 mothers with available data, 1697 (67.4%) were primigravida. At the time of registration, 29.1% of the children were unable to walk without assistive devices, 30.3% had severe intellectual impairment, 10.4% had severe visual impairment, and 1.7% severe hearing impairment. Nine hundred and forty-five children (23.9%) were known to have been admitted to a neonatal care unit. Apgar score at five minutes had been recorded since 1990 in four registers, and was available for 761 children. Among them, 610 (80.2%) had an Apgar score ≥ 7 and 57 (7.5%) scored below 4.

Change over time in characteristics of children with cerebral palsy and birthweight ≥ 2500g (Table 2)

There was no significant change in the proportion of children with CP who were female, or from a multiple birth. The mean Z score for birthweight increased significantly. Mean maternal age increased from 26.7 years to 28.8 years, $P<.001$. The proportion of children with severe intellectual impairment decreased from 33.4% in 1980-1984 to 27.9% in 1995-1998, but the trend did not reach significance.

Prevalence of cerebral palsy in children with birthweight ≥ 2500g

The overall prevalence, including 14 registers, was 1.14 per 1000 births (CI, 1.09–1.18) during the study period. Prevalence rates in each register are presented in Table 3. For 12 of them, trends in prevalence were not significant. Two registers from United Kingdom showed significant change in prevalence: an increase was seen in the area covered by Newcastle register, SCPE_C08 (P=.01) whilst a decrease was observed in Oxford register, SCPE_C09 (P<.001).

When analyzing trend in overall prevalence of CP in Europe, there was a significant interaction between register and birth year (P<.001). This interaction indicates that the trend was heterogeneous across registers and therefore does not allow reporting of an overall trend for all registers. After removing the two registers (Newcastle and Oxford) which showed a significant trend in prevalence, the interaction was no longer significant (P=.83). We therefore analyzed trends pooling data from the 12 remaining registers whilst data from Oxford and Newcastle were analyzed separately. The overall prevalence for the 12 registers was 1.10 per 1000 live births (1.05−1.15) from 1980 to 1998; 1.16 per 1000 live births (CI, 0.88−1.48) in 1980 and 0.99 per 1000 live births (CI, 0.80−1.20) in 1998 (Figure 2). The decrease was not significant (P=.14). The prevalence of bilateral spastic CP decreased significantly from 0.58 (CI, 0.41−0.80) in 1980 to 0.33 (CI, 0.22−0.46) in 1998, P<.001. At the same time, the prevalence of unilateral spastic CP increased from 0.37 (CI, 0.23−0.58) to 0.46 (CI, 0.34−0.62), P=.004. There was no significant change in the prevalence of dyskinetic forms over the period, P=.37. The prevalence of moderate-to-severe CP decreased from 0.52 (CI, 0.34−0.75) to 0.42 (CI, 0.30−0.57) but the trend was not significant (P=.009). The prevalence of mild cases was stable (P=.67) with a mean rate of 0.53 per 1000 live births (CI, 0.50−0.56).

In Newcastle, the prevalence increased significantly (Figure 3, *P*=.01), mainly because of the increase in bilateral spastic type (*P*=.005) from 0.54 per 1000 (CI, 0.18−1.27) to 0.71 (CI, 0.44−1.08). There were no significant changes in rates of other CP subtypes or in the moderate-to-severe group. In Oxford, the prevalence decreased significantly (Figure 3, *P*<.001), mainly due to a decrease in unilateral spastic type from 0.37 (CI, 0.18−0.66) to 0.16 (CI, 0.05−0.37), *P*=.006. In this register, there was a "borderline" decrease in bilateral spastic forms, *P*=.06 and a decrease in the prevalence of moderate-to-severe forms, *P*=.02.

During the same period covered by our study, i.e. between 1980 and 1998, there was a significant reduction in neonatal mortality of nearly 50% from 1.7 (CI, 1.4−2.1) to 0.9 (CI, 0.7−1.1) per 1000 NBW live births in the areas covered by registers which contributed data throughout (n=9).

DISCUSSION

The SCPE population-based registers and surveys feed a unique population-based database for Europe using standardized procedures to include and classify children with CP. In the present study, we found that in 12 out of 14 registers, there was no significant change in prevalence of CP in children with birthweight ≥ 2500 g born between 1980 and 1998. Our findings issuing from population-based data are unlikely to be influenced by a selection bias typically encountered in hospital-based studies. And this result is in agreement with previous studies conducted outside Europe. A recent report from the Western Australia cerebral palsy register [4] showed stable trends in prevalence of CP in NBW children, with a prevalence slightly higher than we observed (1.55 per 1000 live births in 1980-1984 to 1.62 in 1995-1999). A study from California, USA, also reported a stable prevalence of CP in term children of 1.1 per 1000 live births in 1991-2002.[17] Robustness of our results was assessed in analyzing prevalence rates and trends of CP in children born at term (≥ 37 gestational age) in the 11 registers able to provide population data by gestational age. Results were very similar to those observed on NBW children (data not shown). Obviously, data quality of the SCPE common database remains dependent on the quality of data provided by the contributing registers. Some of them have already shown the reliability of their data in previous studies, [27-30] and continuous data quality improvement work is being performed at the network level.

The clinical profile of children with CP was generally stable over time. However, there was a non-significant trend toward a decrease in the frequency of associated impairments, i.e. severe intellectual impairment and, in the last period, severe visual impairment. Twenty-four percent of the children were known to have been admitted to a

neonatal care unit. This percentage may be an underestimate due to numerous missing data in three registers. Two recent studies in the USA and Australia showed that 30% to 35% of children born at term who developed CP were admitted to a neonatal intensive care unit (NICU).[17, 31] Whilst most moderate (1500 g to 2499 g) or very low birthweight children are born in maternity with NICU, this is not observed for NBW children. The significant decrease in neonatal mortality for NBW children reflects advances in obstetric and neonatal care between 1980 and 1998 and it is reassuring that this was not accompanied by a rise in CP prevalence. Probably the impact on morbidity of these improvements in neonatal care is first seen in children born in maternity with NCIU. The significant decrease in CP prevalence seen in very low birthweight [32] children is yet to be observed in NBW children.

Several explanations can be proposed regarding the different trends observed in two UK registers. In Oxford, the decline in prevalence was particularly marked for births after 1996. We can not exclude a true decline in the number of children with CP in this area. However, this was more likely the result of under-ascertainment due to the unwillingness of clinicians to provide data for the CP register following the enactment of the 1998 Data Protection Act. Both in Scotland and Liverpool registers have ceased collecting data because of these difficulties. Moreover, the register in Northern Ireland was allowed to move to a non-consent based system because of incompleteness when seeking consent. The explanation for the observed increase in Newcastle may be related to the expansion of its catchment area from 1991 births. If the prevalence for the additional area covered since 1991 was higher than the pre-1991 area, the inclusion of this additional area may have increased the overall prevalence. This explanation is supported by the stability of prevalence over the period 1964-1993 in the initial catchment area.[33]

We observed a significant decrease in the bilateral spastic group, the most common subtype, of more than 40%. At the same time, there was an increase in unilateral spastic subtype. It is unlikely that the changes in prevalence of unilateral and bilateral CP types resulted from classification bias between the two subtypes. A reliability study performed in 2003 within the SCPE network showed more discrepancies between bilateral spastic and dyskinetic CP than between bilateral and unilateral spastic CP.[34] However, we do not believe that the trends reflect a different approach to classification of dyskinetic and bilateral spastic as there was no significant change in the prevalence of dyskinetic CP. In addition, if the increase in unilateral spastic CP was related to improved ascertainment, an overall increase in milder cases could be expected and this was not observed. Few papers have analyzed trends over time by CP subtypes and birthweight and usually it is proportions of subtypes that are compared, not prevalence.[9,][33] In our study, we found a non-significant increase in prevalence of dyskinetic forms. A recent study, also based on the SCPE common database, reported a significant increase in the prevalence of dyskinetic CP among NBW children for the period 1976-1984, followed by a plateau. [35] Our analysis covered a later period, 1980-1998, and confirmed the leveling off of prevalence of dyskinetic CP.

The changes observed in spastic subgroups do not have a straightforward interpretation. We agree with recent comment of Pharoah, regarding the fact that trends in incidence, not prevalence are crucial to determining etiology. [36] Nevertheless, few hypothesis might be mentioned. The decrease in prevalence of bilateral spastic CP may be explained by improvements in neonatal care, but there is no obvious reason for the increase in unilateral spastic CP. Neuro-imaging studies [10, 11]suggest that slightly different patterns of brain abnormalities are observed in unilateral and bilateral spastic CP. Thus, it might be possible that prevention has affected the two subtypes differently.

In conclusion, this study was the first to analyze European trends in prevalence of CP in children with birthweight ≥ 2500 g. We showed that the prevalence was stable in spite of decreasing neonatal mortality. The reduction in prevalence of bilateral spastic CP, suggests that prevention of the more severe forms may be occurring. Data were available for children born until 1998, thus ongoing monitoring of the trends, including trends in the different subtypes, is necessary.

ACKNOWLEDGMENTS

We thank all SCPE participants: C Cans, S Rey (RHEOP, Grenoble, FR), J Chalmers (ISDSHS, Edinburgh, UK), V McManus, A Lyons (Lavanagh Centre, Cork, IE), J Parkes, H Dolk (Belfast, UK), P Uvebrant, K Himmelmann (Göteborg University, Göteborg, SW), A Colver (University of Newcastle, Newcastle, UK), J Kurinczuk, G Surman (NPEU, Oxford, UK), I Krägeloh-Mann, V Horber (Tübingen University, Tübingen, DE), MJ Platt (University of Liverpool, Liverpool, UK), P Udall, S Holst-Ravn (NIPH, Copenhagen, DK), MG Torrioli, S Matricardi (Lazio Cerebral Palsy Register, Rome, IT), G Andersen, A Meberg (CPRN, Tonsberg, NO), M Bottos (Bologna, IT), G Gaffney (Galway, IE), J De la Cruz, C Pallas (DIMAS-SAMID, Madrid, SP).

FUNDING

This work was supported by grants from the European Commission [Research DG-QLG5-2001-30133, DGSANCO-2003-3131]. Geraldine Surman was funded by the Policy Research Programme in the Department of Health, England and the views expressed are not necessarily those of the Department.

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Table 1. Characteristics of children with cerebral palsy and birthweight ≥ 2500 g, summary from 14 SCPE registers[a] (n=3948).

	N=3948 (%)
Male	58.0
Gestational age (2.2 % missing)	
< 37 weeks	8.8
37-41 weeks	83.3
> 41 weeks	7.9
Maternal age in years, mean (SD) (28.3% missing)	27.8 (5.6)
Multiple births (1.9 % missing)	2.6
CP type (3.9% missing)	
Bilateral spastic	45.7
Unilateral spastic	39.2
Dyskinetic	9.3
Ataxic	5.8
Walking (8.3% missing)	
Without assistive devices	57.1
With assistive devices	13.7
Unable to walk	29.1
Epilepsy (15.0% missing)	36.9
Severe intellectual impairment (IQ<50) (13.1% missing)	30.3
Known to have a severe visual impairment	10.4
Known to have a severe hearing impairment	1.7
Known to have been admitted to a neonatal care unit	23.9
Severity (7.7% missing)	
Severe (IQ<50 and unable to walk, even with assistive devices)	20.0
Moderate (IQ<50 and able to walk or IQ≥50 and unable to walk without assistive devices)	29.5
Mild (IQ≥50 and able to walk without assistive devices)	50.5

[a] Data from Tübingen registering only bilateral spastic cases were excluded

Table 2. Changes over time in characteristics of children with cerebral palsy and birthweight ≥ 2500g. From 14 SCPE registers (n=3948).

Characteristics [a]	1980-1984 *n*=758	1985-1989 *n*=1252	1990-1994 *n*=1057	1995-1998 *n* =881	Test for linear trend [b] *P value*
Female, n (%)	344 (45.4)	530(42.3)	427 (40.4)	357 (40.5)	.06
Maternal age over 34 years, n (%)	51 (9.5)	91 (10.5)	111 (15.2)	111 (15.7)	.001
Multiple birth, n (%)	21 (2.9)	22 (1.8)	30 (2.8)	26 (3.0)	.15
Z score, mean (SD)	-0.25 (1.22)	-0.15 (1.31)	-0.06 (1.36)	0.08 (1.42)	<.001
Unable to walk, even with aids, n (%)	203 (28.2)	380 (30.9)	286 (27.8)	185 (28.8)	.77
Severe intellectual impairment, n (%)	226 (33.4)	303 (29.5)	300 (30.9)	211 (27.9)	.05
Severe visual impairment, n (%)	78 (10.6)	140 (11.9)	129 (12.3)	65 (7.4)	.29
Severe hearing impairment, n (%)	8 (1.1)	30 (2.4)	17 (1.6)	12 (1.4)	.56
Epilepsy, n (%)	214 (37.9)	343 (35.2)	391 (38.6)	291 (36.2)	.98
Severe-to-moderate CP, n (%)	350 (50.2)	598 (51.5)	474 (47.8)	383 (48.2)	.42

[a] Mother's age was available for 2831 children, multiple birth status for 3872 children, Z score for 3763 singleton children, ability to walk for 3621 children, intellectual impairment level for 3433 children, epilepsy for 3357 children. Percentages are calculated using the total known cases for each characteristic as denominators

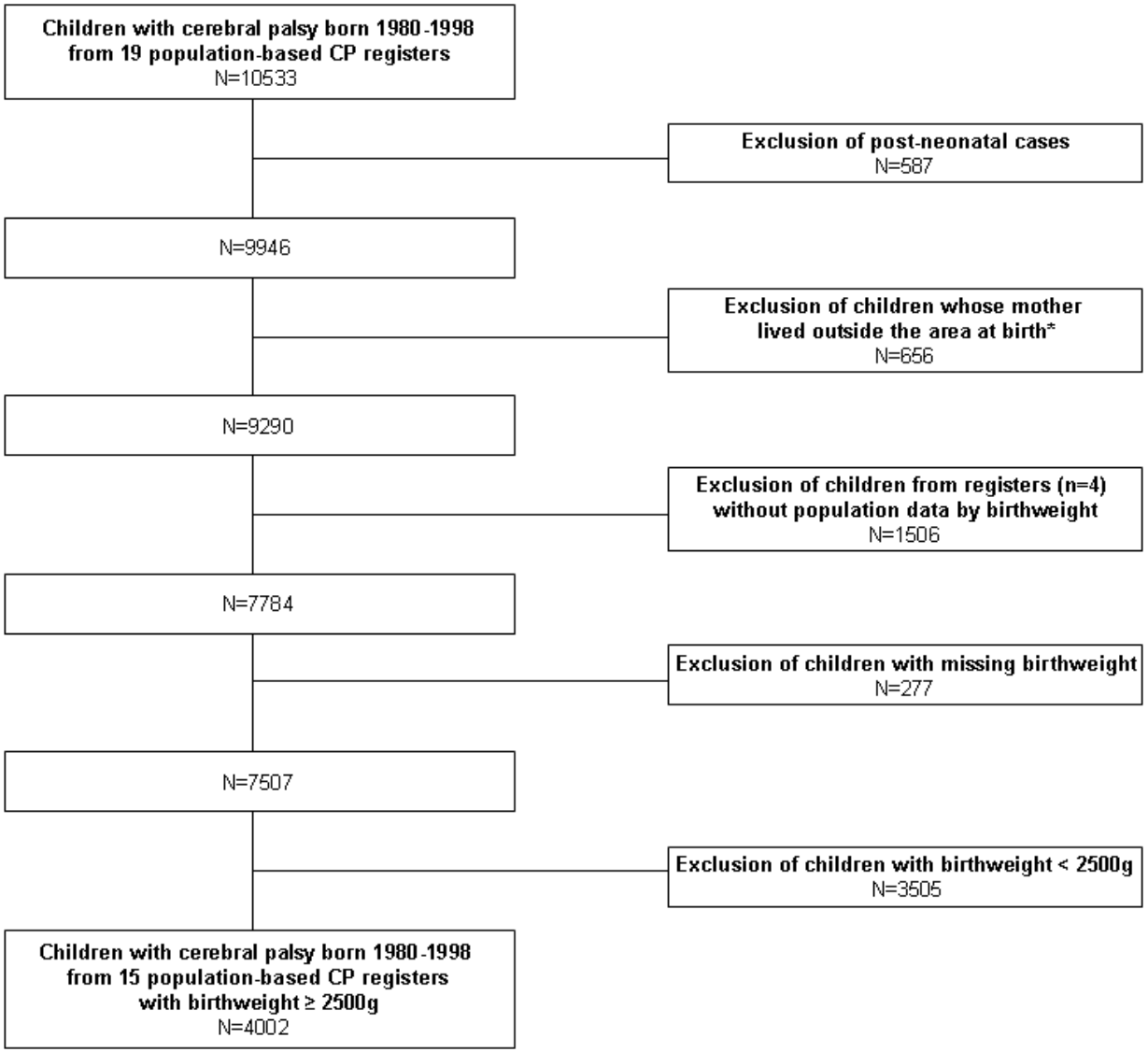
[b] Test for linear trend was adjusted for register

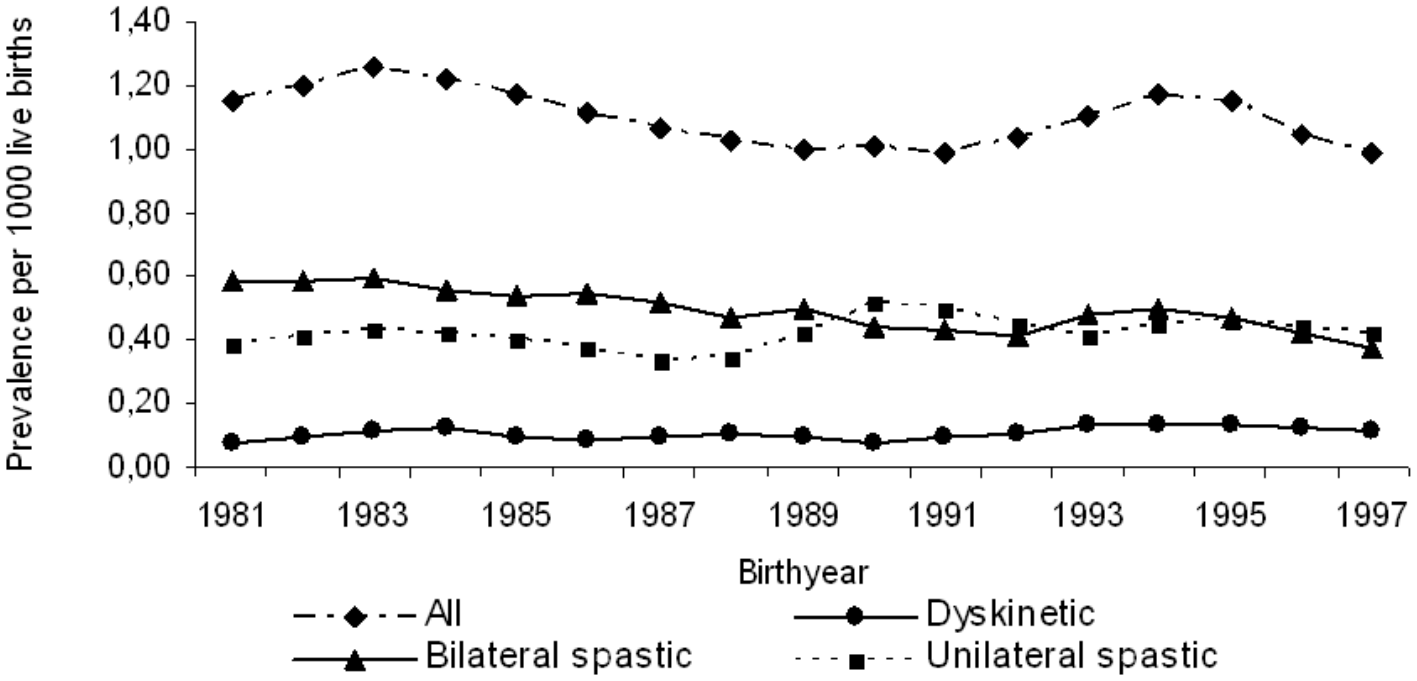
Table 3. Children with cerebral palsy and birthweight ≥ 2500g by SCPE register: number of cases and prevalence by period.

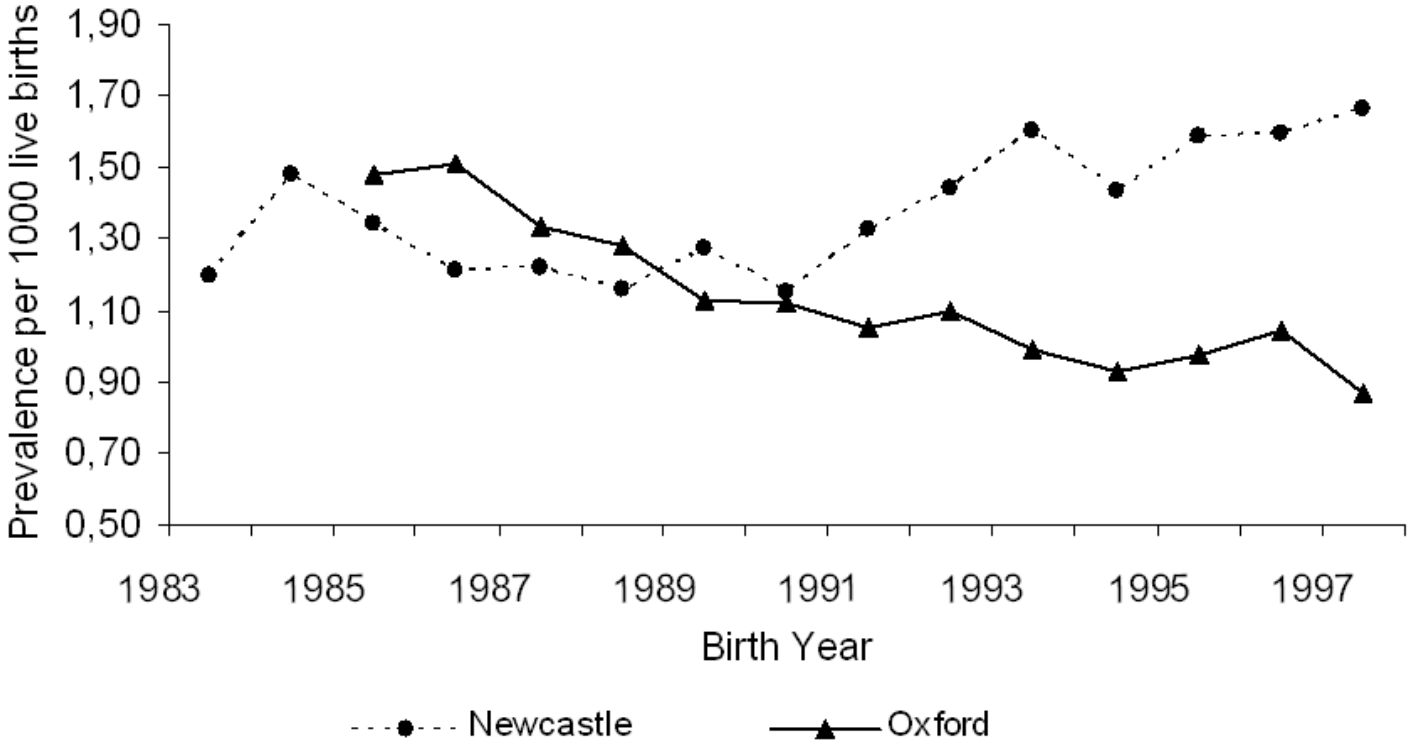
	Period covered	Number of cases	Prevalence rate [a] 1980-1984	Prevalence rate [a] 1985-1989	Prevalence rate [a] 1990-1994	Prevalence rate [a] 1995-1998
Grenoble, France (SCPE_C01)	1980-1998	234	0.88	0.99	1.21	0.80
Edinburgh, UK (SCPE_C03)	1984-1989	301	0.83	0.83	–	–
Cork, Ireland (SCPE_C04)	1986-1998	89	–	0.96	0.93	0.91
Belfast, UK (SCPE_C05)	1981-1998	472	1.21	1.04	1.16	1.13
Gothenburg, Sweden (SCPE_C06)	1980-1998	474	1.32	1.32	1.19	1.16
Newcastle, UK (SCPE_C08)	1980-1998	501	1.09	1.27	1.42	1.55
Oxford, UK (SCPE_C09)	1984-1998	543	1.28	1.40	1.00	0.88
Tübingen, Germany (SCPE_C10)[b]	1980-1986	*54*				
Liverpool, UK (SCPE_C11)	1980-1989	340	1.23	1.26	–	–
Copenhagen, Denmark (SCPE_C12)	1980-1998	738	1.46	1.30	1.25	1.29
Rome, Italy (SCPE_C13)	1983-1998	40	1.54	1.20	1.24	0.62
Tonsberg, Norway (SCPE_C15)	1991-1998	98	–	–	1.05	0.89
Bologna, Italy (SCPE_C16)	1991-1996	25			0.74	0.69
Galway, Ireland (SCPE_C17)	1990-1998	62			0.83	1.16
Madrid, Spain (SCPE_C18)	1991-1998	31			0.65	0.72

[a] Prevalence rates are presented per 1000 live births

[b] The SCPE_C10 register included only children with bilateral spastic cerebral palsy.


Children with cerebral palsy born 1980-1998
from 19 population-based CP registers
N=10533
Exclusion of post-neonatal cases
N=587
N=9946
Exclusion of children whose mother
lived outside the area at birth*
N=656
N=9290
Exclusion of children from registers (n=4)
without population data by birthweight
N=1506
N=7784
Exclusion of children with missing birthweight
N=277
N=7507
Exclusion of children with birthweight < 2500g
N=3505
Children with cerebral palsy born 1980-1998
from 15 population-based CP registers
with birthweight ≥ 2500g
N=4002


Prevalence per 1000 live births
1,40
1,20
1,00
0,80
0,60
0,40
0,20
0,00
1981
1983
1985
1987
1989
1991
1993
1995
1997
Birthyear
All
Dyskinetic
Bilateral spastic
Unilateral spastic


Prevalence per 1000 live births
1,90
1,70
1,50
1,30
1,10
0,90
0,70
0,50
1983
1985
1987
1989
1991
1993
1995
1997
Birth Year
Newcastle
Oxford