Decreasing prevalence in cerebral palsy: a multi-site European population-based study, 1980 to 2003

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The Surveillance of Cerebral Palsy in Europe (SCPE) network was formed in 1998. It established a common database of individual data on those with CP with data contributed by population-based CP registers across Europe using agreed classifications, definitions, and shared quality assurance processes. It has previously described trends in CP prevalence by birthweight and gestational age groups in the pooled data set, demonstrating a decline in CP prevalence among children with birthweight below 1500g, from 60.6 in 1980 to 39.5 per 1000 live births in 1996. For children born between 32 weeks and 36 weeks,

Cerebral palsy (CP) is the most common cause of significant motor impairment in children. It has many determinants, generally classified according to their time of onset: antenatal, perinatal, or postnatal. It is commonly perceived to result from multiple interacting factors and events rather than a single cause. Changes in obstetric and neonatal practices over time have led to the expectation that the likelihood of a child developing CP will also change. In response to this, many areas established population-based registers to monitor CP prevalence, with the aim of relating changes in prevalence to changes in antenatal, perinatal, and postnatal care.

A recent systematic review and meta-analysis estimated the prevalence of CP at 2.11 per 1000 live births among children born since 1985. The authors concluded that the prevalence has not changed significantly in recent years, basing their conclusion on recently published studies. Prevalence estimation from meta-analysis of aggregated data from studies with heterogeneous inclusion and exclusion criteria is less robust than from estimation based on pooled individual data with homogeneous criteria. Furthermore, this study did not assess population changes over time, nor examine time trends within birthweight or gestational age specific groups. A recent review comparing prevalence trends, in CP overall and by gestational age groups from 1970 to 2004, drew on data from different population-based registers worldwide. However there are many challenges in the interpretation of differences or similarities when registers do not share the same harmonization methods. To our knowledge, there has been no recent published report of prevalence trends using pooled individual data from multisite population-based registers using an agreed data protocol.

The decline in prevalence of CP in children of VLBW continues, and confirms that previously reported. For the first time, there is also a significant decline among children born between 32 weeks and 36 weeks.
the prevalence declined in a non-linear pattern between 1980 and 1998. The peak prevalence observed in 1983 was 12.2 per 1000 live births and was followed by a decrease. No significant change in prevalence has been reported in children with moderately low birthweight (MLBW, 1500–2499g). Similarly, no significant change in the prevalence for children born with a normal birthweight (NBW, >2499g) has been reported, with a mean prevalence of 1.14 per 1000 between 1980 and 1998.

There has been no recent, large-scale, population-based study exploring time trends in CP prevalence. The study reported here aims to address this by analyzing data on CP by birthweight groups in Europe among children born between 1980 and 2003.

METHOD
Definition and classification
The registries participating in the SCPE network are population-based and cover either a part or a whole country in Europe. Data collection and harmonization methods have been previously reported. CP is defined as a group of permanent, but not unchanging, disorders of movement and/or posture and of motor function, caused by a non-progressive interference, lesion, or abnormality of the developing/immature brain. Progressive disorders or non-cerebral diseases leading to a loss of motor function are excluded. The diagnosis of CP should be confirmed at around age five. Subtypes of CP were recorded as unilateral spastic, bilateral spastic, dyskinetic, or ataxic. Severity of disability was defined, using available data from participating registries on intellectual quotient (IQ), Gross Motor Function Classification System (GMFCS), and walking ability, and classified as either moderate-to-severe (children with IQ <50 or in GMFCS levels III to V or not able to walk without assistive devices) or mild (children with IQ ≥50 and either in GMFCS levels I to II or able to walk without assistive devices). To ensure data harmonization across countries, the SCPE network developed several tools including hierarchical trees, a standardized data collection form, and a reference and training manual CD-ROM translated into 12 languages. For a full description, go to http://www.scpenetwork.eu.

Study population
In total, 26 population-based registers provided anonymized individual data to the SCPE common database for the whole or part of the period 1980 to 2003, representing 15 090 children with CP (Fig. 1). The children were categorized in four birthweight groups: <1000g (extremely low birthweight, ELBW), 1000 to 1499g (very low birthweight, VLBW), 1500 to 2499g (moderately low birthweight, MLBW), and >2499g (normal birthweight, NBW). Inclusion criteria were as follows: (1) children whose mothers lived in an area covered by a register at the time of birth (except for Grenoble [France], where important migration patterns led us to include the children living in the area at the time of registration instead); and (2) children registered in registers with annual population data for live births, stratified by birthweight, available for some or all of the study period. Exclusion criteria were: children with a post-neonatal onset; children from registries with a poor level of (1) completeness; and (2) children from registries with data on only one CP subtype or from registers with only 1 year of registration data. Data on neonatal deaths stratified by birthweight were provided by 10 registers and used in the results as an estimate for neonatal mortality in Europe during the study period. Data from a further six registries unable to provide such data were excluded.

The SCPE network has no specific ethical approval as it only gathers anonymized data. Each register had its own ethical approval that follows the legislative rules of its country.

Statistical analysis
To study changes in the birthweight distribution of children with CP, we compared three time periods: 1980 to 1987, 1988 to 1995, and 1996 to 2003, using the $\chi^2$ test on register effect.

Prevalence rates are presented throughout the article per 1000 live births for all cases and for each birthweight group. To analyze trends over time, Poisson models were used with prevalence rates as outcome variables. The models were adjusted for birth year, register, and offset term to account for denominator. These models allowed us to study the trends including data from registers unable to contribute data for the entire study period. Heterogeneity of trends between registers was tested in adding an interaction term between register and birth year, using the median trend as the reference trend. In case of significant interaction, the register(s) responsible for interaction was (were) excluded. We also tested non-linearity of the trends using orthogonal polynomial terms for birth years up to the third order. Likelihood-ratio $\chi^2$ tests were used to compare nested models.

To analyze the trends in prevalence, we also fitted mixed effects models. These yielded similar results as those presented in this article, i.e. without random effects.

The threshold was $p<0.005$ for overall analyses and $p<0.05$ for analyses of individual registers data. Figures 3a to 3d show the birth prevalence of all CP and of moderate-to-severe CP in each birthweight group. Curves were smoothed using locally weighted scatterplot smoothing. Statistical analyses were performed using stata Statistical software (version 12.0; StataCorp., College Station, TX, USA).

RESULTS
A total of 10 756 children with CP from 20 registers covering a population of 5 382 785 inhabitants were included.
in the analysis (Table I). The prevalence of CP in 18 registers decreased linearly from 1.90 (99% CI 1.57–2.28) in 1980 to 1.77 (1.57–1.99) in 2003, \(p<0.001\), a mean decrease of 0.7% per annum (95% CI –0.3% to –1.0%). Two registers (Slovenia and Portugal) showed significantly different trends from the others \(p\) for interaction <0.001), each with a decrease more pronounced than the other registers. When restricting the analysis to the children with moderate-to-severe CP, there was no significant interaction, and a significant decline in prevalence was observed across the 20 registers, from 0.98 (99% CI 0.75–1.26) to 0.72 (0.61–0.83), \(p<0.001\), a mean annual fall of 1.8% per annum (95% CI –1.2% to –2.3%).

Figure 2 shows the birthweight distribution among children with CP across three time periods. In the most recent time period (1996–2003) the proportion of both NBW and ELBW increased, with a concomitant decrease in those of MLBW \(p<0.001\). Within the ELBW group, the proportion of those <750g increased from 12\% (14/117) in 1980 to 1987 to 33\% (125/375) in 1996 to 2003 \(p\) for trend=0.002), and within the VLBW group, 48\% (729/1530) had a birthweight between 1000 to 1250g with no

**Figure 1:** Flow chart.

**Figure 2:** Birthweight distribution of children with cerebral palsy born between 1980 and 2003 in European registers. ELBW, extremely low birthweight; VLBW, very low birthweight; MLBW, moderately low birthweight; NBW, normal birthweight.
significant change over time \((p=0.91)\). The distribution of CP subtype by birthweight (Table II) showed a significant change over time only among the spastic group, with a decrease in the proportion with bilateral spastic CP and a concomitant increase in the proportion with unilateral spastic subtype in both MLBW and NBW groups \((p<0.001)\).

Data on IQ were missing for 1760 children \((16.4\%)\) and GMFCS/walking for 597 children \((5.6\%)\). Data on severity were missing for 1201 children \((11.2\%)\). By period, severity was missing for 10.5% of children in 1980 to 1987, 7.8% of children in 1988 to 1995, and 13.8% of children in 1996 to 2003.

The overall prevalence of CP among NBW children was 1.13 \((5492/4,872,419)\), with a non-statistically significant decrease from 1.17 \((99\%\ CI 0.90–1.49)\) to 0.89 \((0.77–1.03)\), \(p=0.22\) (Fig. 3a). The peak prevalence was 1.34 \((1.08–1.64)\) in birth year 1983. The moderate-to-severe CP subgroup also showed a non-statistically significant decrease, from 0.52 \((0.34–0.74)\) to 0.39 \((0.31–0.48)\), \(p=0.02\). During the same period, neonatal mortality for NBW children decreased significantly from 1.65 \((CI 1.33–2.03)\) to 0.89 \((0.75–1.05)\) per 1000 live births \((p<0.001)\).

Among NBW children, the prevalence rate of children with bilateral spastic CP decreased significantly, with a mean annual fall of 1.4% per annum \((95\%\ CI –0.7% to –2.1%)\), \(p<0.001\), falling from 0.64 \((0.49–0.83)\) to 0.35 \((0.29–0.42)\). The prevalence rate of children with unilateral spastic CP increased significantly but not linearly, \(p=0.003\). The peak prevalence was 0.55 in 1991 \((0.44–0.66)\), followed by a plateau until 2000 and then a tendency to decrease.

The overall prevalence of CP among MLBW children was 9.4 \((2336/249,393)\). It fell from 8.5 \((99\%\ CI 5.4–12.7)\) to 6.2 \((4.9–7.8)\), \(p<0.001\), over the study period, although not linearly with a peak prevalence in 1983 (Fig. 3b). For the moderate-to-severe CP, the prevalence decreased from 4.5 \((2.3–7.7)\) to 3.2 \((2.3–4.4)\), \(p<0.001\); but again this was not linear, with a peak prevalence in 1988. During the same period, neonatal mortality for MLBW children decreased from 19.6 \((14.7–25.6)\) to 9.3 \((7.4–11.4)\) per 1000 live births \((p<0.001)\). Among MLBW children, the prevalence rate of children with bilateral spastic CP decreased significantly but not linearly \((p=0.001)\). The peak prevalence was 9.3 \((7.0–12.2)\) in 1983 and the lowest 3.7 \((2.9–4.6)\) in 2003. The prevalence rate of children with

Figure 3: (a) Prevalence rate of cerebral palsy (CP) for children born with a birthweight \(\geq 2500\)g, per 1000 live births. (b) Prevalence rate of CP for children born with a birthweight between 1500g and 2499g, per 1000 live births. (c) Prevalence rate of CP for children born with a birthweight between 1000g and 1499g, per 1000 live births. (d) Prevalence rate of CP for children born with a birthweight below 1000g, per 1000 live births. NBW, normal birthweight; MLBW, moderately low birthweight; VLBW, very low birthweight. ELBW, extremely low birthweight.
Innsbruck, Austria 1990–1999
Pecs, Hungary 1990–1999
Riga, Latvia 1990–1999
Lisbon, Portugal 1990–1999
Ljubljana, Slovenia 1990–1999
Madrid, Spain 1990–1999
Galway, Ireland 1990–1999
Bologna, Italy 1990–1999
Tonsberg, Norway 1990–1999
Rome, Italy 1990–1999
Copenhagen, Denmark 1990–1999

Birthweight 1000 to 1499g (VLBW), birthweight; BS-CP, bilateral spastic cerebral palsy; US-CP, unilateral spastic cerebral palsy.

The overall CP prevalence for ELBW children was 42.4 (76/18008), ranging from 40.9 (99% CI 12.1–97.3) in 1980 to 38.2 (260–33.8) in 2003 (Fig. 3d). There was no significant trend (p=0.84) with non-linear increase until 1992. For the moderate-to-severe CP, the prevalence was also stable, with a mean of 20.0 (SD 7.0). From 1980 to 2003, neonatal mortality for ELBW children decreased from 632 (531–725) to 316 (279–345) per 1000 live births (p=0.001), i.e. a 75% reduction.

Eight registers were active during all three time periods (Grenoble [France], Cork [Ireland], Belfast [UK], Göteborg [Sweden], Dublin [Ireland], Newcastle [UK], Tonsberg [Norway], Rome [Italy]) and collected data on 7464 of the children included in the SCPE common database. The analyses of trend restricted to these eight registries showed similar results as those found when using data from all registers participating in SCPE.

**DISCUSSION**

The analysis presented here provides an updated estimate of the prevalence of CP in Europe for the birth years 1980 to 2003, and is the first paper to show a significant decrease in both the overall prevalence of CP within Europe, and in the prevalence of moderate-to-severe CP. It shows a significant reduction in the prevalence of CP among children of birthweight 1500 to 2499g (MLBW), and demonstrates a further reduction in the prevalence of CP in children with birthweight 1000 to 1499g (VLBW) compared with that reported previously (1980–1996). Although CP prevalence is still considerably higher in the lower birthweight groups, these findings provide important feedback to obstetricians and neonatologists, and for child health systems in general, particularly as the decreased prevalence of CP among VLBW and MLBW infants accompanies a neonatal mortality in at least 50% across Europe. Although similar significant reductions are not also seen in NBW and ELBW groups, they are not increasing. Thus the work of SCPE, particularly when set alongside a continued decline in neonatal mortality rates in these groups and a more important decline in the moderate-to-severe group, provides an encouraging message to both clinicians and parents. Among those of ELBW, the group considered at greatest risk of CP, the proportion of babies born with a birthweight of <750g,
Epidemiological data from other countries and continents

To our knowledge, in the United States, there are no published data of recent trends in CP prevalence by birthweight groups. The most recent report from The Metropolitan Atlanta Developmental Disabilities Surveillance Program, which monitors trends in childhood developmental disabilities, indicates a CP prevalence rate of 3.1 per 1000 8-year-old children in 2008, showing little change from the rate reported in 2002. Using data from the National Health Interview Surveys, CP prevalence showed a small increase from 3.9 to 4.3 per 1000 (1997–2002). However, in this study, information on CP was parent-reported, without confirmation from a clinical source.

A follow-up study of extremely preterm babies (<28wks) born in Alberta, Canada reported similar CP prevalence and neonatal mortality rates to those reported here, but data on less premature babies is not available for this population. In another Canadian province (Nova Scotia), while mortality rates declined between 1993 and 2007, CP rates in children born <31 weeks showed a steady increase until period 1998 to 2002, followed by a decrease. SCPE data are best compared with data from the Australian Cerebral Palsy Register (ACPR). The ACPR monitors CP prevalence over time, using data from several Australian registers, and uses inclusion and exclusion criteria, and a CP classification system similar to those used by SCPE. Their recent report, on children born 1993 to 2006, showed similar trends in birthweight-specific CP prevalence, although the decrease in the VLBW group was only observed from birth year 1998. They also show a declining prevalence in the ELBW group, although this may reflect a different birthweight distribution within this ELBW group. Thus, data from two different continents with similar health care systems, and using similar methods suggest that the observed change in CP prevalence, even on a general level, is unlikely to be because of chance.

Neonatal care

Over the period of study included in this paper, there have been many critical developments implemented in neonatal care. For very preterm born children, the 1990s saw an increasing use of steroids, in both the antenatal and postnatal period (until recommendations from paediatric academies and societies lead to a decline in their postnatal use). Other important changes include the introduction of surfactant, and improvement in the management of nosocomial infections. Overall, it is clearly recognized that these changes have led to a reduction in both mortality and impairment. However, among ELBW infants, although the evolution of neonatal practice has had a significant effect on neonatal mortality, the effect on reduction of impairment is less evident. The results of the Epicure studies demonstrated that 20% of all babies born at 22 to 25 weeks’ gestation in 2006 had a severe disability, and that this proportion remained unchanged since 1995. For term-born children, the introduction of hypothermia treatment for hypoxic–ischaemic encephalopathy after severe asphyxia is clearly a milestone in their care. There is increasing evidence that its use is resulting in a decrease not only in mortality but also in CP. This treatment is now being used more widely, thus a potential reduction in CP prevalence among those of NBW group relating to this treatment would not yet be reflected in our analyses, which covered only birth years until 2003.

Pathogenetic factors

The global view, of an unchanging overall CP prevalence, has led in recent years to a discussion of genetic factors, and whether they may play a more important role in the pathogenesis of CP than previously considered. However, several systematic reviews on magnetic resonance imaging (MRI) findings in children with CP indicate that brain maldevelopments, which may be due to monogenetic diseases, only account for approximately 10% of pathology in children with CP. These reviews report that the most prevalent imaging findings among those with CP, accounting for 50 to 60% of cases, were white matter lesions such as periventricular leukomalacia (PVL) or sequelae of haemorrhage. They are typically lesions of the more immature brain and are especially seen in children born preterm with CP (e.g. in around 90%). From hospital-based studies, there is evidence for a decrease over time in PVL. described a decrease in cystic PVL of more than 50% between birth periods 1990 to 1993 and 2002 to 2005. The most significant decrease (10-fold) was seen in the severe form, i.e. cystic PVL III. In contrast to PVL, there is no clear evidence for a decrease of severe intraventricular haemorrhage (IVH) in the preterm infant during the same period. PVL is typically bilateral, thus, when it affects the motor tracts, it usually gives rise to bilateral spastic CP. In contrast, severe IVH or haemorrhagic infarction usually have a unilateral impact on motor tracts and, thus, give rise to unilateral spastic. These data also suggest that on a population basis, a decrease of CP in children born preterm, especially bilateral spastic, could be anticipated. Indeed, already our earlier papers have suggested this now confirmed in the data until birth year 2003, presented here.

The MRI findings in NBW children with CP are more heterogeneous. Findings suggestive of a prenatal origin of CP, e.g. maldevelopments of the brain or white matter lesions are predominant (around 15% and 20% respectively). Patterns that are compatible with an origin around the term account for around 30%. These include infarcts, where there is no evidence that peri- or neonatal care would influence their occurrence, and lesions associated with hypoxia–ischaemia after asphyxia and neonatal encephalopathy. The latter lesions arising in <20% of
NBW children with CP are the only ones where neonatal care, such as hypothermia treatment could be expected to have an impact on CP prevalence. Thus, expectations for a change in CP prevalence, relating to changes in the neonatal management of such infants, will necessarily only address a small part of prevalence observed in children born at term. It will be interesting to note any changes in the prevalence of CP in this group in the future. For some factors associated with CP among children born at term, i.e. non-central nervous system abnormalities, placental status, young maternal age or socio-economic status, there are still inconsistencies in the literature, and more population-based studies on larger numbers of children should be performed, with international collaborative work allowing for meta-analysis of these factors. It has to be recognized, however, that in nearly one-third of children born at term it is reported that no specific risk factors were present, i.e. much more often than among children born preterm (9%).

Methodological considerations
The data used for this analysis were provided by 20 population-based registers from Europe, all members of the SCPE network, with a long history of harmonizing data, and sharing data collection methods and inclusion/exclusion criteria. Robust methods for analyzing multi-centre data and identifying ‘outliers’ were used. In addition, confidence in the results presented here is enhanced by the fact that the same trends were observed when restricted to the group of children with moderate-to-severe CP. Although the severity was not possible to assess for 11% of the children, this is unlikely to have biased our results. Indeed the lowest percentage of missing was seen in 1988 to 1995 and we observed a linear decrease in the moderate-to-severe prevalence rate.

The time lag between the last birth cohort included in the analysis and the publication date of this paper is because of the age of confirmation of the diagnosis of CP and the practice of registration of CP in epidemiological studies to delay registration until aged 4 to 5 years. Further delay occurs due because of the stringent data validation procedures established at both the individual register level and at SCPE central registry level. The unavailability of information on live birth denominators by birthweight group in some of the administrative areas covered by the individual registers prevented performing the inclusion of all SCPE network registries in this analysis. The lack of centre-specific information for live births denominators by gestational age has made analysis by gestational age groups unfeasible at this stage.

CONCLUSION
Continued collaboration of registers within the SCPE network has made it possible to demonstrate time trends in CP prevalence. CP prevalence has decreased in children born with moderately and VLBW, even in the presence of decreasing neonatal mortality. This paper has shown, for the first time, a decrease in the overall prevalence of CP, with a decrease of almost 2% per annum in moderate-to-severe CP. This paper has also shown how data on neonatal mortality and the prevalence of CP can improve understanding of the impact of improvements in neonatal care. The introduction of a method to systematically record the results of brain imaging in children with CP may help to further understand mechanisms behind the changes in prevalence.

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