Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study

Mary Jane Platt, Christine Cans , Ann Johnson, Geraldine Surman, Monica Topp, Maria Giulia Torrioli, Inge Krageloh-Mann

Summary

Background **The risk of cerebral palsy, the commonest physical disability of children in western Europe, is higher in infants of very low birthweight (VLBW)—those born weighing less than 1500 g—and those from multiple pregnancies than in infants of normal birthweight. An increasing proportion of infants from both of these groups survive into childhood. This paper describes changes in the frequency and distribution of cerebral palsy by sex and neurological subtype in infants with a birthweight below 1000 g and 1000–1499 g in the period 1980–96.**

Methods **A group of 16 European centres, Surveillance of Cerebral Palsy in Europe, agreed a standard definition of cerebral palsy and inclusion and exclusion criteria. Data for children with cerebral palsy born in the years 1980–96 were pooled. The data were analysed to describe the distribution and prevalence of cerebral palsy in VLBW infants. Prevalence trends were expressed as both per 1000 livebirths and per 1000 neonatal survivors.**

Findings **There were 1575 VLBW infants born with cerebral palsy; 414 (26%) were of birthweight less than 1000 g and 317 (20%) were from multiple pregnancies. 1426 (94%) had spastic cerebral palsy, which was unilateral (hemiplegic) in 336 (24%). The birth prevalence fell from 60·6 (99%CI 37·8–91·4) per 1000 liveborn VLBW infants in 1980 to 39·5 (28·6–53·0) per 1000 VLBW infants in 1996. This decline was related to a reduction in the frequency of bilateral spastic cerebral palsy among infants of birthweight 1000–1499 g. The frequency of cerebral palsy was higher in male than female babies in the group of birthweight 1000–1499 g (61·0 [53·8–68.·2] *vs* 49.5 [42·8–56·2] per 1000 livebirths; p=0·0025) but not in the group of birthweight below 1000 g.**

Interpretation **These data from a large population base provide evidence that the prevalence of cerebral palsy in children of birthweight less than 1500 g has fallen, which has important implications for parents, health services, and society.**

Lancet 2007; 369: 43–50

See **Comment** page 7

Division of Public Health, Whelan Building, University of Liverpool, Liverpool L69 3GB, UK (M J Platt MB); **Registre des Handicaps de l'Enfant et Observatoire Périnatal-Technologies de l'Imagerie de la Modélisation et de la Cognition, Pavillon Taillefer, Grenoble, France** (C Cans PhD); **National Perinatal Epidemiology Unit, University of Oxford, Oxford, UK** (A Johnson MD, G Surman MSc); **Cerebral Palsy Registry, National Institute of Public Health, Copenhagen, Denmark and Department of Obstetrics and Gynaecology, Hvidovre Hospital, Copenhagen, Denmark** (M Topp MD); **Universita' Cattolica Del Sacro Cuore Facolta' di Medicina e Chirurgia Agostino Gemelli, Rome, Italy** (Prof M G Torrioli MD); **and Department of Child Neurology, University Children's Hospital, Tübingen, Germany** (Prof I Krageloh-Mann MD)

Correspondence to:
Dr Mary Jane Platt
mjplatt@liv.ac.uk

Introduction

Cerebral palsy is the commonest disability of children in western Europe, with a birth prevalence of about two cases per 1000 livebirths. Studies of the patterns of cerebral palsy in relation to birthweight show that infants of very low birthweight (VLBW—ie, less than 1500 g), are between 20 and 80 times more likely to have cerebral palsy than infants of birthweight more than 2500 g.[1] Data from Sweden, Australia, and the UK suggest that the prevalence of cerebral palsy among VLBW infants increased during the 1980s,[2–4] and data from the northeast of England[5] and the USA,[6] seem to show a rise in severity of cerebral palsy in this group of infants. Studies from Denmark,[7] Oxford, UK,[8] Sweden,[9] and Liverpool, UK[4] suggest that the prevalence of cerebral palsy in VLBW infants has begun to fall, although studies from other centres in Australia,[3,10] and Atlanta, GA, USA,[11] have not shown a fall. Decreased neonatal mortality of VLBW infants is related to improved care of premature infants and has also changed perceptions of viability of these infants. There has also been an increase in multiple births over this period.[12] These changes have resulted in a rise in the absolute number of VLBW infants at risk of cerebral palsy.

Previous studies describing the distribution, determinants, and clinical picture of cerebral palsy in VLBW infants included small numbers of infants, which reduced the precision of results and did not allow detailed investigation of the various subtypes of cerebral palsy. Even less information is available about the subset of infants who weighed less than 1000 g at birth (whose survival also improved substantially since the 1980s).[13,14] Thus, little is known about the distribution of cerebral palsy by sex, severity, or neurological subtype in such small infants. Birthweight-specific differences might reflect different origins; very immature infants could be more vulnerable to white-matter damage of different extent and topography than more mature infants and could also be less susceptible to primary cortical damage.[15]

A collaborative network of cerebral palsy registers and surveys, Surveillance of Cerebral Palsy in Europe (SCPE), was established in 1998. The 16 European centres in this network have developed a standard definition of cerebral palsy (with inclusion and exclusion criteria), and have agreed definitions and descriptions of affected children.[1] On the basis of these definitions, the prevalence of cerebral palsy among VLBW infants was calculated as 72·6 per 1000 neonatal survivors (children who survived for longer than 1 month after birth), compared with a prevalence of 1·2 per 1000 among infants of birthweight more than 2500 g.[16] The 16 centres provide a large study population, which gives an opportunity to examine the distribution, determinants, and clinical patterns of cerebral palsy among VLBW children.

This collaboration showed a non-significant downward trend in the overall prevalence of cerebral palsy at the end of the 1980s,[1] and with reports from individual centres suggesting a reduction in prevalence and severity of cerebral palsy among VLBW infants,[8,17] the hypothesis that the birthweight-specific prevalence of cerebral palsy among VLBW infants will have remained stable or fallen further during the 1990s, is reasonable. This paper aims: to describe the epidemiology of cerebral palsy in VLBW infants in detail, looking at those of birthweight less than 1000 g separately from infants of birthweight 1000–1499 g, where possible; to examine changes in the prevalence of cerebral palsy in these two groups over the period 1980–96; and to identify whether the two birthweight groups differ in terms of sex, severity, or neurological subtype.

Methods

The collaboration of centres with data from population-based studies on the prevalence of cerebral palsy in nine European countries has previously been described.[1] Case definitions and inclusion and exclusion criteria were agreed in these centres, and data for children with cerebral palsy from 16 European surveys and registers were pooled in a common SCPE dataset. Cerebral palsy was defined as a permanent, but not unchanging, disorder of movement or posture, or both, and of motor function, caused by a non-progressive interference, lesion, or abnormality in the brain. Children with hypotonia but no other neurological signs were excluded.[1] Since motor disorders in young children generally change over time, some children with severe cerebral palsy have the diagnosis confirmed within the first year of life, but others, especially those less severely affected, might not have the diagnosis confirmed until later in childhood.

Most population-based cerebral palsy surveys and registers do not include children until they are at least 3 years old to ensure full ascertainment. This approach also means that the clinical picture of each child with cerebral palsy can be described accurately (eg, whether the child can walk, the degree of intellectual and other associated impairment). Affected children were at least 4 years old at the time of inclusion in the SCPE database. This analysis included children who were born with cerebral palsy between 1980 and 1996, whose birthweight was known, and whose mothers lived in an area covered by the survey or register at the time of birth or registration of birth. Children with cerebral palsy linked to a specific event or episode that happened after 28 days of age (postneonatal origin) were excluded. Population data for livebirths and neonatal deaths, by birthweight and by gestational-age were requested from each centre, for the years it contributed data to the SCPE dataset.

This study looked at demographic characteristics of mother (age and parity), child (sex, weight, and gestational age at birth) and whether the child was from a multiple pregnancy; the neurological subtype of cerebral palsy (spastic [unilateral or bilateral], dyskinetic, or ataxic), and measurements of each child's function (ability to walk, intelligence quotient [IQ], vision, and hearing). Severe cerebral palsy was defined as inability to walk, even with aids, and with an IQ of less than 50 (measured or clinician's impression). Severe visual impairment was defined as a clinical diagnosis of blind or near blind. Hearing loss was defined as more than 70 dB in the best ear.

Statistical methods

Exact CI were calculated with Stata (version 8.0). Time trends were examined by individual years if data allowed, or in 4 or 5-year cohorts (1980–83, 1984–87, 1988–91, and 1992–96).[1] When data for livebirths and neonatal deaths stratified by birthweight or gestational age were available, prevalence of cerebral palsy was calculated to allow the rates to be expressed per 1000 neonatal survivors as well as per 1000 livebirths. Stratification by birthweight and sex was also possible for some centres. A threshold of $p<0\cdot005$ was used for significance (to allow for multiple hypothesis testing) and in view of the large numbers in the dataset, to guard against identification of statistically significant findings that were not clinically significant, 99% CI were calculated. For data from individual centres, 95% CI were calculated. Centre 10 (Tübingen, Germany) provided data only for children with bilateral spastic cerebral palsy, and these data were included only in the analysis of this particular subgroup.

A Z score was derived for each child, by use of the north of England birthweight standard,[18] a widely used standard calculated from more than 118 000 singleton, non-malformed births (antepartum stillbirths were excluded) from the 1980–96 period. Children with cerebral palsy from singleton births were compared with this standard separately by sex.

In models used to test trends over time, prevalence was the outcome variable, and the models were adjusted for birth year and centre as potential confounders. The data were tested for any centre effect and for interactions between birth year and centre. If a centre effect was present, year effect was tested after adjustment by centre in a multivariate model. If interaction was present, the birth year effect on this prevalence (ie, overall trend over time) was tested and is given here adjusted by the centre effect, if the latter was significant.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

16 centres contributed data for children with cerebral palsy to the SCPE database, which covered births in years

Location of centre	Centre	Data available	Number of cases <1000 g	Number of cases 1000–1499 g	Number of cases ≥1500 g and <32 weeks[1]*	Total
Isére, France	C 01	1980–96	9	57	24	90
Haute Garonne, France	C 02	1981–93	0	20	13	33
Scotland, UK	C 03	1984–90	38	117	54	209
Cork and Kerry, Ireland	C 04	1981–95	11	27	16	54
Northern Ireland, UK	C 05	1981–96	74	130	60	264
Göteborg, Sweden	C 06	1980–96	34	101	50	185
East Ireland, Ireland	C 07	1980–93	31	53	39	123
Northern Region, UK	C 08	1980–96	55	98	42	195
Oxford, UK	C 09	1984–96	58	141	55	254
Tübingen, Germany†[2]	C 10	1980–86	14	28	7	49
Mersey Region, UK	C 11	1980–89	36	123	38	197
East Denmark, Denmark	C 12	1980–96	49	201	105	355
Viterbo province, Italy	C 13	1981–95	9	19	12	40
Gelderland, Netherlands	C 14	1981–89	3	14	11	28
Tonsberg, Norway	C 15	1991–96	1	4	1	6
Bologna, Italy	C 16	1991–96	6	14	1	21
	Total		428	1147	528	2103

*Also includes cases of <32 weeks' gestation with unknown birthweight. †Centre provides data only on cases with bilateral spastic CP.

Table 1: **Description of SCPE data on children with cerebral palsy included in the study**

1980–96, although not all centres were actively collecting data in all birth years. There were 7884 children with cerebral palsy born between 1980 and 1996 (after exclusion of those with cerebral palsy of post neonatal origin), whose mothers were resident in an area covered by the register at the time of birth or birth registration. Of these children, 2103 (26·6%) were of birthweight less than 1500 g or of gestational age less than 32 weeks at the time of birth, and formed the study population for subsequent analyses (table 1).

There were significant differences by sex, *Z* score, and the proportion with unilateral spastic cerebral palsy between the birthweight groups (table 2).

Between 1980 and 1996, in VLBW infants, the mean birthweight of affected children fell from 1169 g to 1094 g (75 g fall, p=0·0004). Children from both Northern Ireland and east Ireland had significantly lower birthweight than those from other centres, after exclusion of centre 10 (49 children), and controlling for year effect. There was a similar, significant difference in mean gestational age

	Birthweight <1000g (n=414)	Birthweight 1000–1499g (n=1119)	Birthweight ≥1500g, <32/40 (n=521)	p
Number of male children	203 (49%)	619 (55%)	326 (63%)	<0·0001
Mean (SD) birthweight, g	840 (114)	1249 (143)	1721 (228)	<0·0001
Mean (SD) gestational age, weeks	26·7 (2·1)	29·3 (2·1)	30·0 (1·1)	<0·0001
Mean maternal age in years (SD)	27·9 (5·7)	27·4 (5·7)	28·1 (5·8)	0·154
Primigravida	206 (70%)	632 (69%)	269 (64%)	0·178
Mean (SD) *Z* score	−0·56 (1·15)	−0·23 (1·08)	1·0 (1·29)	<0·0001
Number of children known to have died	9 (2%)	16 (1%)	14 (3%)	0·16
Number of multiple births	85 (21%)	232 (21%)	80 (15%)	0·086
Number with spastic cerebral palsy	380 (93%)	1046 (94%)	488 (95%)	0·595
Number with unilateral spastic cerebral palsy	111 (29%)	225 (21%)	88 (18%)	0·0003
Number with severe cerebral palsy	53 (13%)	146 (13%)	64 (12%)	0·991
Number with severe visual impairment	57 (15%)	119 (11%)	47 (10%)	0·062
Number who have seizures	40 (12%)	98 (11%)	43 (10%)	0·662
Number with hearing loss	42 (11%)	81 (8%)	24 (5%)	0·008

*Centre 10 provided data only on cases with bilateral spastic cerebral palsy (49 children) and are excluded from this table.

Table 2: **Summary of characteristics of cerebral palsy among children of birthweight less than 1000 g, of 1000–1499 g and of those of birthweight 1500 g but gestational age less than 32 weeks[1]***

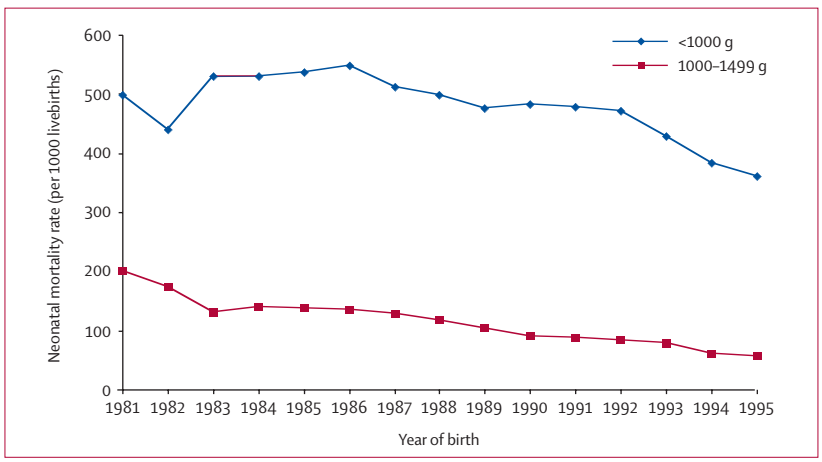

Figure 1: **Birthweight-specific neonatal mortality rates in eight European centres that contributed to SCPE collaboration, 1981–95**

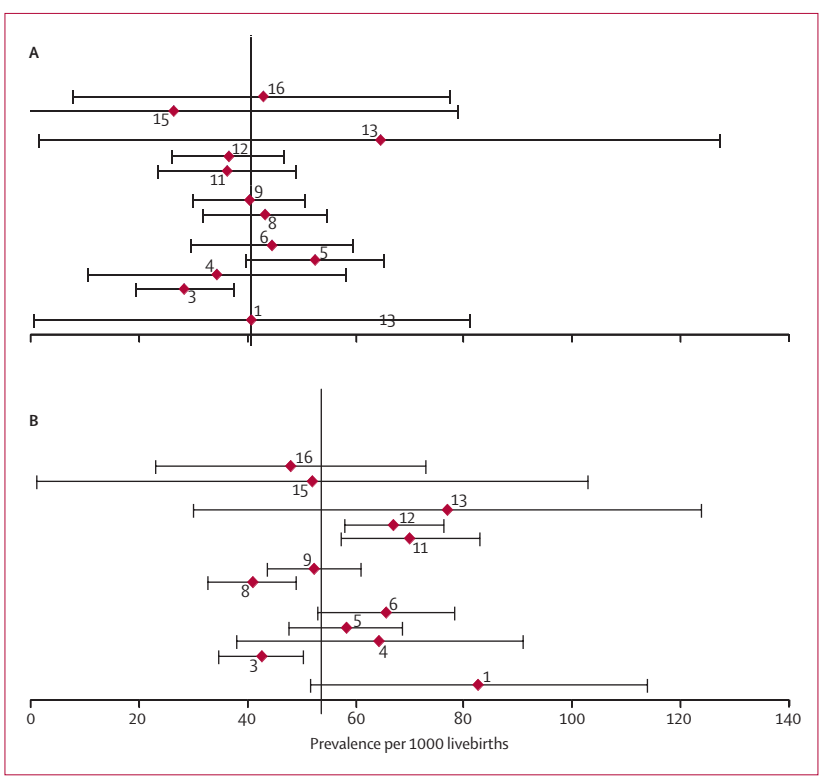

Figure 2: **Birthweight-specific cerebral palsy rate (per 1000 livebirths) by SCPE centre, 1980–96, with 95% CI shown for each centre**

(A) Children of birthweight <1000 g. (B) Children of birthweight 1000–1499 g. Solid vertical line indicates the birthweight-specific rate of cerebral palsy (per 1000 livebirths) for the total study population, and the horizontal lines indicate 95% CI.

(30·0 weeks *vs* 29·5 weeks; p<0·0001). Both trends remained significant after adjustment for centre. However, there was no significant change in *Z* score over this time.

In children of VLBW, there was no significant change with time in the proportion of male children with cerebral palsy, in the proportion of children with spastic cerebral palsy, or in the proportion of children with unilateral spastic cerebral palsy. The proportion of children with severe cerebral palsy did not change over the duration of the study. The proportion of VLBW children from multiple births with cerebral palsy increased significantly over the study period, from 17% (40/230) in the period 1980–83 to 24% (87/324) (χ^2 test for linear trend; p=0·004).

In all centres, the proportion of VLBW births among livebirths has increased since 1980.This increase was highest in UK centres and in Sweden, from 0·5% (109/1946) in 1980 to almost 1% (133/19009) in 1996. The proportion of VLBW infants increased significantly (p<0·0001) over time, after we had taken into account centre differences and excluded the Danish centre (C12) where there was a significant decrease among singleton VLBW births (p=0·003) although the overall proportion of VLBW infants remained steady.

The neonatal mortality rate has fallen since 1980. A significant decrease in the VLBW-specific neonatal mortality rate was seen in most of the eight centres that provided data for this variable. Among infants with a birthweight of less than 1000 g the neonatal mortality rate fell from 50% to 35% (p<0·0001), and among those with a birthweight of 1000–1499 g it fell from 20% to 5% (p<0·0001) (figure 1). The decline in neonatal mortality rate in babies of birthweight less than 1000 g was smaller in Denmark.

The overall prevalence of cerebral palsy in VLBW children during the study period (1314 children, with centre 10 excluded) was 50·6 per 1000 livebirths (99% CI 47·2–54·2). In the group of children with birthweight less than 1000 g (353 children), the prevalence of children with cerebral palsy was 40·0 per 1000 livebirths (34·8–45·7) and in the group of birthweight 1000–1499 g (961 children) the prevalence was 56·1 per 1000 livebirths (51·6–60·8; figure 2). This difference in prevalence remained significant after adjustment for centre (p<0·0001). Prevalence also differed by sex; in 450 boys of birthweight 1000–1499 g, the prevalence was 61·0 per 1000 livebirths (53·8–68·2) compared with 49·5 per 1000 livebirths (42·8–56·2) in 344 girls (p=0·0025). There was no difference in prevalence by sex among children of birthweight less than 1000 g; the prevalence was 39·5 per 1000 livebirths (31·1–49·0) for 140 boys and 37·1 per 1000 livebirths (29·1–45·1) for 137 girls of the same birthweight (p=0·59).

There was a significant fall in the prevalence of cerebral palsy among VLBW infants over the study period from 60·6 per 1000 livebirths (37·8–91·4) in 1980 to 39·5 (28·6–53·0) in 1996 (p<0·0004), which remained significant after adjustment for centre. The significant decline in prevalence was restricted to the group of children with birthweight 1000–1499 g. Figure 3 shows that this decline varied over time, with a steep fall in the prevalence in the first 5 years (1980–85), then a plateau phase (1986–89), before another fall in the later years (1990–96). The decline is mainly explained by a reduction in the prevalence of bilateral spastic cerebral palsy among children of birthweight 1000–1499 g (717 children); the

prevalence was 64·2 per 1000 livebirths (38·5–99·2) in 1980, and fell to to 29·4 (17·6–45·5) in 1996 (figure 4). In children of birthweight less than 1000 g (240 children), there was no significant change in prevalence over the 17-year period (figure 3). Rates of unilateral spastic cerebral palsy were similar in both birthweight groups (9·2 of <1000 g and 11·0 of 1000–1499 g), and these rates remained steady during the study period.

In children of birthweight 1000–1499 g, there was a significant decline in the rate of cerebral palsy with inability to walk (p=0.001), which matches the reduction in overall cerebral palsy rate. The proportion of children with cerebral palsy who were unable to walk does not seem to have changed over time in either birthweight group. Although most of the fall in cerebral palsy prevalence can be attributed to a reduction in the frequency of bilateral spastic cerebral palsy, the clinical profile of children with this form was constant for the duration of the study period, with 35% (32–39) of affected children unable to walk and 24% (99%CI 20–27) with an IQ of less than 50.

To take into account the changes in neonatal mortality over the period and their effect on the prevalence of cerebral palsy, particularly among children of birthweight less than 1000 g, cerebral palsy rate per 1000 neonatal survivors was calculated for centres able to provide birthweight-specific population data on neonatal death (centres 3, 6, 8, 9, 11, 12, and 15). For VLBW infants (996 children), the overall rate was 64·8 per 1000 neonatal survivors (59·8–70·1); it fell from 90·4 per 1000 (55·3–136·4) in 1980 to 44·1 per 1000 (27·7–66·1) in 1996. Neonatal survivors in the group of birthweight less than 1000 g (258 children) had a cerebral palsy rate of 74·3 per 1000 children (63·3–86·5), compared with 62·1 (56·5–68·0) in the group of birthweight 1000–1499 g (738 children). The pattern of cerebral palsy prevalence per 1000 neonatal survivors in the higher birthweight group is similar to that seen in the prevalence per 1000 livebirths (p<0·0001), (figure 3). By contrast, the pattern per 1000 neonatal survivors in the group of birthweight less than 1000 g differed from that seen in livebirth prevalence, showing a non-significant decrease over the study period,

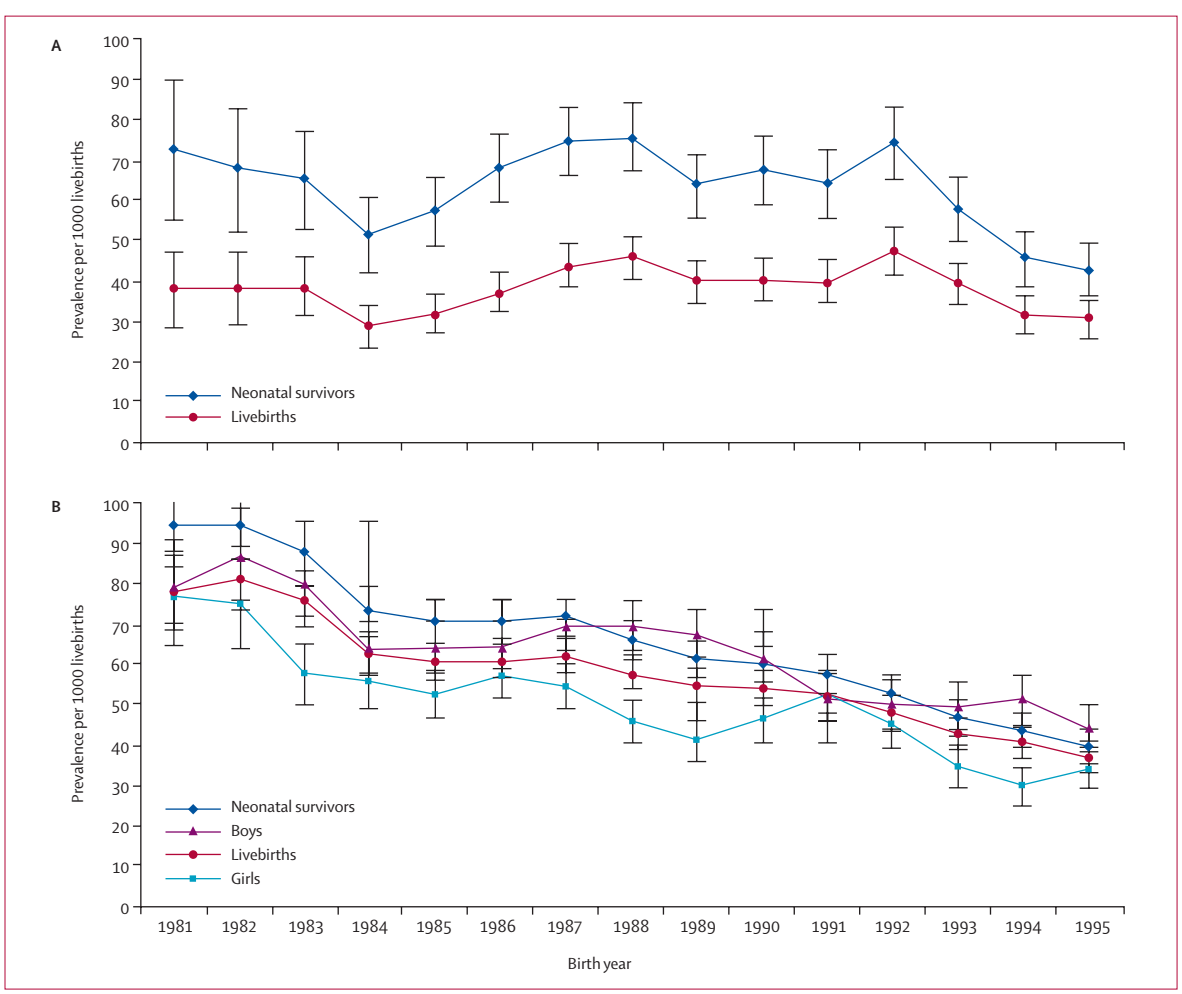

Figure 3: **Cerebral palsy rates (3-year moving average) among infants of birthweight <1000 g (A) and 1000–1499 g (B) from nine European centres, 1980–96**
Error bars=SE.

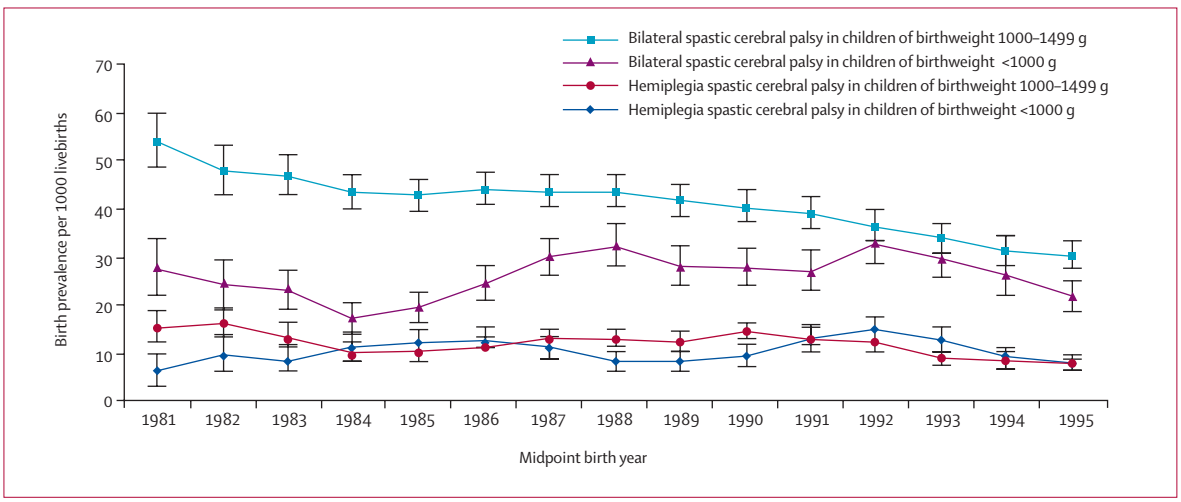

***Figure 4*: Birthweight-specific birth prevalence of bilateral and unilateral spastic cerebral palsy (3-year moving average) from nine European centres, 1980–96**
Error bars=SE.

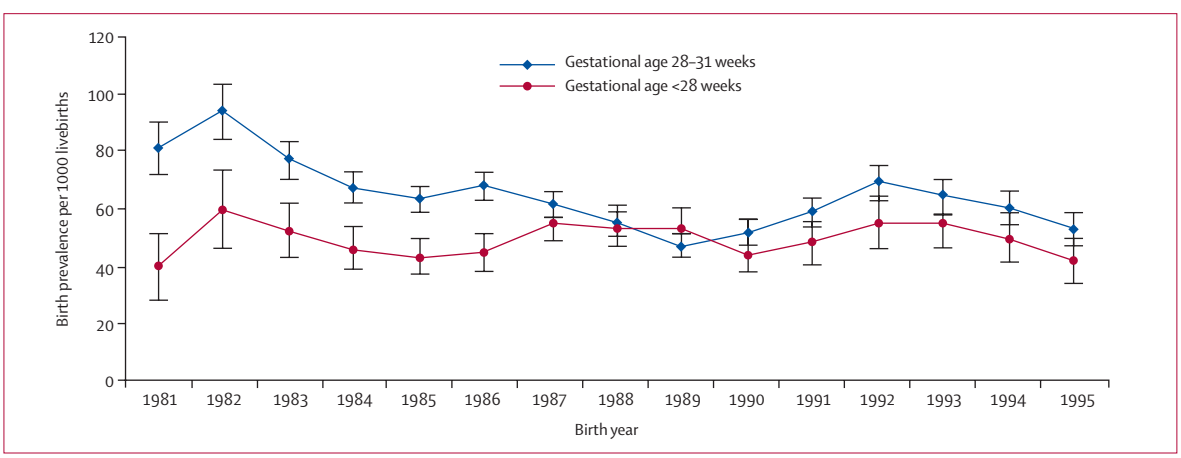

***Figure 5*: Gestational-age-specific birth prevalence of cerebral palsy (3-year moving average), from nine European centres, 1980–96**
Error bars=SE.

with most of the fall in prevalence among infants of birthweight less than 1000 g who were born after 1990 (p=0·039, figure 3).

Population data stratified by gestational age were available for fewer centres than population data by birthweight. In 868 children from six centres, the prevalence of cerebral palsy for those born before 32 weeks of gestation was 58·0 per 1000 livebirths (53·1–63·1). Among 203 children born before 28 weeks' gestation, the prevalence of cerebral palsy was 48·6 per 1000 livebirths (40·5–57·8); this rate was significantly lower (p=0·002) than that of infants born at 28–31 weeks' gestation (665 children), who had a prevalence of 61·1 per 1000 livebirths (55·8–67·8). This difference remained significant after adjustment for year and centre of birth. Among infants born before 28 weeks' gestational age, there was no significant trend over time, but among those born at 28–31 weeks' gestation, there was a significant fall in prevalence (p<0·0001) between 1981 and 1995 (figure 5).

Discussion

Our findings are unlikely to be subject to selection bias associated with hospital-based studies because the data come from population-based centres. This study shows that the survival of infants of birthweight less than 1500 g continues to improve and that this continued improvement is not accompanied by increased morbidity. Although other studies have reported no change in the cerebral palsy rate over time among VLBW survivors to 1 year born between 1975 and 1991,[11] the data presented here for a similar period show a decline in the rate of cerebral palsy among such infants, especially of bilateral spastic cerebral palsy. Rates of other subtypes remained steady. This decline was seen initially only in infants of birthweight 1000–1499 g, but in the most recent period, the decline was also apparent in infants of birthweight less than 1000 g. Although ascertainment could have varied between centres children with bilateral spastic cerebral palsy are generally the most severely affected

and their ascertainment is unlikely to vary. The rigorous harmonisation procedures undertaken before data pooling[16] should ensure that the results represent true findings rather than methodological errors.

The changes in the rate of cerebral palsy by gestational age follow those of birthweight, with a significant fall over the period for children born at 28–31 weeks' gestation. The absence of a significant trend in infants of less than 28 weeks' gestation, adds to the evidence that a shift in the proportion of small-for-gestational-age infants is not an explanation for the fall in prevalence of cerebral palsy. We cannot explore in more detail the relation between birthweight and maturity, because we do not have denominator information in gestational-age bands stratified by birthweight.

Among children with cerebral palsy of birthweight less than 1500 g, the mean birthweight and gestational age has fallen slightly over the 17-year period, and the mean *Z* score remained the same, which suggests that infants who develop cerebral palsy are born slightly earlier in pregnancy and are light for that reason. The change in prevalence of cerebral palsy is not related to a change in the frequency of VLBW infants who are born small for their gestational age.

What is less clear is whether these findings suggest a reduction in the risk of cerebral palsy in infants of slightly greater maturity at delivery or reflect a change in clinical practice resulting in the earlier delivery of infants already at risk of cerebral palsy—for example, showing antenatal signs of distress. Clarke and colleagues[19] have argued that an increase in survival of infants with cerebral palsy is unlikely to have resulted from the more active management of intrapartum asphyxia, since the increase in the number of caesarean sections done because of fetal distress would be too small to have a detectable effect on the cerebral palsy rate.[19]

Over the period of this study, there have been many changes in the care and management of VLBW infants; These changes happened at different times in the different centres in this collaboration. Thus, the trends reported here cannot be associated with the introduction or withdrawal of specific perinatal management strategies—eg, antenatal steroids and surfactant therapy. Clinical trials and hospital-based follow-up studies are needed to assess the effects of perinatal interventions.[4,20,21] This paper provides an overview of the effect of neonatal intensive care over 17 years. Evidence suggests that part of the reduction seen in the prevalence of cerebral palsy is a result of general improvements in neonatal care; comparison of the rate per 1000 livebirths with the rate per 1000 neonatal survivors shows the strong effect on the denominator for cerebral palsy rates, mainly during the first half of the study period. Among infants born weighing 1000–1499 g, the difference between the rate of cerebral palsy per 1000 neonatal survivors and prevalence per 1000 livebirths was 20% at the beginning of the period and only 3% by the end of the study period, which shows that nearly all the liveborn infants in this birthweight group survived for at least a month. Among infants with birthweight less than 1000 g, the difference between the rate per 1000 neonatal survivors and the prevalence among all livebirths was 50%, which decreased to 20% by 1996.

Additionally, there was large and probably random variation in the rate per 1000 neonatal survivors in the lowest birthweight group resulting from the small number of infants with cerebral palsy, which probably affected the precision of estimates of rates in the early years of the study. Later, when a greater number of infants in this birthweight group survived, this variation became less influential, as shown by the non-significant downward trend in the rate of cerebral palsy per 1000 neonatal survivors in infants of birthweight less than 1000 g in the most recent years studied. Fewer centres were able to provide birthweight-specific data for neonatal survivors than were able to provide birthweight-specific data for livebirths, and centres able to provide gestational-age-specific denominators were fewer still. This factor affects the precision of the estimated rates of cerebral palsy per 1000 neonatal survivors and prevalence of cerebral palsy by gestational age. However, although the relation between the provision or otherwise of these denominators and quality of prenatal care is uncertain, there is no evidence to suggest a significant source of bias that would affect the trends reported here.

The denominator data also showed an increasing rate of VLBW per 1000 livebirths, which might be a result of changes in recording of births around viability, with decreasing numbers of stillbirths in all countries contributing data to this study.[22] Aggressive resuscitation of premature infants and an increase in the proportion of VLBW infants from multiple births, related to both demographic changes in maternal age and to the increasing use of fertility treatments might also contribute to this trend. The pattern observed in centre 12 (Denmark), of no trend in the rate of cerebral palsy in VLBW infants, and a small fall in neonatal mortality among the VLBW infants, might relate to Denmark having the highest rate of multiple births.[23] Concern has been expressed that the increased rate of multiple births could increase the proportion of children at risk of cerebral palsy.[24] However, the higher proportion of infants with cerebral palsy coming from multiple pregnancies simply parallels the overall rise in the proportion of VLBW infants coming from multiple pregnancies.[25]

This study also showed that among VLBW infants, the male excess in children with cerebral palsy reported previously is seen only in children of birthweight 1000–1499 g, and that this difference by sex is not significant in children with cerebral palsy of birthweight less than 1000 g. Although the absence of a sex difference among the smaller infants might be due to chance, it could suggest a greater survival advantage of female infants in the higher birthweight group, which might not be evident in the group with lowest birthweight and highest mortality. Some

researchers have reported a sex difference in the prevalence of cerebral palsy among infants with birthweight less than 1000 g,[26] but others have reported no difference by sex in adverse neurological outcomes[27] or cerebral palsy[28] in such infants.

The significant reduction in the prevalence of cerebral palsy per 1000 livebirths is mostly due to a reduction in bilateral spastic cerebral palsy among infants of birthweight 1000–1499 g. Prevalence of unilateral spastic cerebral palsy has not changed significantly over the study period. Spastic cerebral palsy in children of birthweight less than 1500 g is predominantly caused by periventricular lesions. Periventricular leucomalacia damages both motor tracts in many cases, thus causing bilateral spastic cerebral palsy, and periventricular haemorrhage mainly causes unilateral motor-tract damage and unilateral spastic cerebral palsy.[15] The prevalence data here suggest a decline mainly of periventricular leucomalacia in children of birthweight less than 1500 g, as reported by Hamrick and colleagues.[21]

In conclusion, this paper presents evidence that infants of birthweight less than 1500 g, and in particular those of birthweight less than 1000 g now have a better chance of survival than previously, and more importantly, a better chance of survival without severe neurological impairment, which demonstrates that improvement in neonatal care has not resulted in increased survival at the cost of substantial morbidity.

Contributors

Mary Jane Platt, Christine Cans, Ann Johnson, and Inge Krageloh-Mann participated in the conception and design of the study. Mary Jane Platt and Christine Cans analysed the data and Mary Jane Platt drafted the manuscript. All authors participated in data acquisition, revision, and critical review, and all have seen and approved the final version.

SCPE participants

C Cans, P S Jouk (Grenoble, France), F Baille, C Arnaud (Toulouse, France), J Chalmers (Edinburgh, UK), V McManus, D Coghlan (Cork, Ireland), J Parkes, H Dolk (Belfast, UK), P Uvebrant, E Beckung (Göteborg, Sweden), O Hensey, V Dowding (Dublin, Ireland), S Jarvis, A Colver (Newcastle, UK), J Kurinczuk, G Surman (Oxford, UK), I Krägeloh-Mann, R Michaelis (Tübingen, Germany), P Pharoah, M J Platt (Liverpool, UK), M Topp, P Uldall, (Copenhagen, Denmark), M G Torrioli, G Schirripai (Rome, Italy), M Wichers (Arnhem, Netherlands), G Andersen, A Meberg (Tonsberg, Norway), M Bottos, A Colonna (Bologna, Italy).

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

This study was supported by European Commission funds (DGXII-BIOMED2-Contrat N°BMH4-983701 and DGXII-FP5-Contrat N°QLG5-CT-2001-30133).

References

1 Surveillance of Cerebral Palsy in Europe. Surveillence of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. *Dev Med Child Neurol* 2000; **42:** 816–24.

2 Stanley F, Blair E, Alberman E. Cerebral palsies: epidemiology & causal pathways. London: MacKeith Press 2000.

3 Doyle LW, Betheras FR, Ford GW, Davis NM, Callanan C. Survival, cranial ultrasound and cerebral palsy in very low birthweight infants: 1980s versus 1990s. *J Paediatr Child Health* 2000; **36:** 7–12.

4 Cooke RW. Trends in incidence of cranial ultrasound lesions and cerebral palsy in very low birthweight infants 1982–93. *Arch Dis Child Fetal Neonatal Ed* 1999; **80:** F115–17.

5 Colver AF, Gibson M, Hey EN, Jarvis SN, Mackie PC, Richmond S. Increasing rates of cerebral palsy across the severity spectrum in north east England 1964–1993. The north of England collaborative cerebral palsy survey. *Arch Dis Child Fetal Neonatal* Ed 2000; **83:** F7–12.

6 Vohr BR, Msall ME. Neuropsychological and functional outcomes of very low birth weight infants. *Semin Perinatol* 1997; **21:** 202–20.

7 Topp M, Uldall P, Greisen G. Cerebral palsy births in eastern Denmark, 1987–90: implications for neonatal care. *Paediatr Perinat Epidemiol* 2001; **15:** 271–77.

8 Surman G, Newdick H, Johnson A. Cerebral Palsy rates among low-birthweight infants fell in the 1990s. *Dev Med Child Neurol* 2003; **45:** 456–62.

9 Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995–1998. *Acta Paediatr* 2005; **94:** 287–94.

10 Watson L, Stanley F, Blair E, Report of the Western Australia Cerebral Palsy Register. Perth: Western Australia Cerebral Palsy Register, 1999.

11 Winter S, Autry A, Boyle C, Yeargin-Allsopp M. Trends in the prevalence of cerebral palsy in a population-based study. *Pediatrics* 2002; **110:** 1220–1225.

12 The Victorian Infant Collaborative Study Group. Improved outcome into the 1990's for infants weighing 500–999g at birth. *Arch Dis Child Fetal Neonatal Ed* 1997; **77:** F91–94.

13 Pison G, D'Addato AV. Frequency of twin births in developed countries. T*win Res Hum Genet* 2006; **9:** 250–59.

14 O'Shea TM, Klinepeter KL, Golldstein DJ, Jackson BW, Dillard RG. Survival and developmental disability in infants with birthweights of 501–800 grams, born between 1979–1994. *Pediatrics* 1997; **100:** 982–86.

15 Krägeloh-Mann I. Impairment of early brain injury and cortical plasticity. *Exp Neurol* 2004; **190:** S84–90.

16 Surveillance of Cerebral Palsy in Europe. Prevalence and characteristics of children with cerebral palsy in Europe. *Dev Med Child Neurol* 2002; **44:** 633–40

17 Krageloh-Mann I, Hagberg G, Meisner C, et al. Bilateral spastic cerebral palsy—a comparative study between southwest Germany and western Sweden. II: epidemiology. *Dev Med Child Neurol* 1994; **36:** 473–83.

18 Tin W, Wariyar UK, Hey EN. Selection biases invalidate current low birthweight for gestation standards. *Br J Obstet Gynaecol* 1997; **104:** 180–85.

19 Clark SL, Hankins GDV. Temporal and demographic trends in cerebral palsy—fact and fiction. *Am J Obstet Gynecol* 2003; **188:** 628–33

20 Ens-Dokkum M E, Johnson A, Schreuder A M, et al. Comparison of mortality and rates of cerebral palsy in two populations of very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 1994; **70:** 96–100

21 Hamrick S E, Miller S P, Leonard C, et al. Trends in severe brain injury and neurodevelopmental outcome in premature newborn infants: the role of cystic periventricular leukomalacia. *J Pediatr* 2004; **145:** 593–99.

22 Bell R, Glinianaia S V, Rankin J, Wright C, Pearce M S, Parker L. Changing patterns of perinatal death, 1982-2000: a retrospective cohort study. *Arch Dis Child Fetal Neonatal Ed* 2004; **6:** F531–36.

23 Breart G, Barros H, Wagener Y, Prati S. Characteristics of the childbearing population in Europe. *Eur J Obstet Gynecol Reprod Biol* 2003; **111** (suppl 1)**:** S45–52.

24 Scher AI, Petterson B, Blair E, et al. The risk of mortality or cerebral palsy in twins: a collaborative population-based study. *Pediatr Res* 2002; **52:** 671–81.

25 Topp M, Huusom LD, Langhoff–Roos J, Delhumeau C, Hutton JL, Dolk H. Multiple birth and cerebral palsy in Europe: a multicenter study. *Acta Obstet Gynecol Scand* 2004; **83:** 548–53

26 Laptook AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005; **115:** 673–80

27 Piecuch R E, Leonard C H, Cooper B A, Sehring S A. Outcome of extremely low birth weight infants (500 to 999 grams) over a 12-year period. *Pediatrics* 1997; **100:** 633–39

28 Shankaran S, Johnson Y, Langer JC, et al. Outcome of extremely-low-birth-weight infants at highest risk: gestational age ≤24 weeks, birth weight ≤750 g, and 1-minute Apgar ≤3. *Am J Obstet Gynecol* 2004; **191:** 1084–91