

Comparison of mortality and rates of cerebral palsy in two populations of very low birthweight infants

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Abstract

Comparisons of mortality and rates of cerebral palsy in different populations can be confusing. This is illustrated by comparing two populations of very low birthweight infants born in the 1980s, one from the Netherlands, the other from the UK (Oxford region). Although a number of biases were controlled for while comparing two large geographically defined populations, by assessing the survivors at similar ages and describing their health status in a standard way, some problems in interpretation of outcome remained. Differences in registration practice of live births at early gestational ages, as well as differences in withholding or withdrawing treatment, which occurred in about half of the cases of neonatal death in the Netherlands and in about one third of those in the Oxford region, may have influenced the incidence of registered live births, neonatal mortality, and the rate of cerebral palsy.

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It is widely recognised that through the 1980s changes in intensive care for fetuses and newborn infants have resulted in a sharply increasing survival rate, particularly among infants weighing less than 1500 g at birth.^{1,2} There is, however, some concern about the later health and wellbeing of those low birthweight infants who survive. This concern arises partly from the results of the systematic follow up of total populations of such infants³⁻⁶ and partly as a result of the trends reported by those who have kept registers of patients with cerebral palsy in a consistent way over many years.⁷⁻¹⁰ The registers show that not only does the rate of cerebral palsy increase with decreasing birth weight but also the birth cohort prevalence of cerebral palsy among infants weighing less than 1500 g at birth has increased in the 1970s and early 1980s.

Mortality is usually considered to reflect level of care, whereas the relation between cerebral palsy and neonatal intensive care is less clear.¹¹ It seems plausible, however, that the recent increase in the rate of cerebral palsy in low birthweight infants may reflect increased chance of survival.

The possible interrelations between mortality and morbidity can be studied by comparing rates of cerebral palsy in populations of infants with different mortalities. For a number of reasons this type of comparison is difficult.

The problems, reviewed by Aylward *et al*¹² and Escobar *et al*,¹³ include those arising from the effects of selection bias in the study of populations defined by admission to particular units, differing denominators such as may occur with variations in the definition of abortion, live birth, and stillbirth, and differing ways of finding and describing the surviving children.

Information on mortality and morbidity among infants born weighing less than 1500 g was collected in two populations, one in the Netherlands and one in the Oxford region (UK). The two populations were defined by residence at the time of birth and the same standard system for describing children with cerebral palsy was used. In this paper we will compare the mortality and morbidity in these two very low birthweight populations, controlling for as many sources of bias as possible.

Methods

INFORMATION ON BIRTHS

The Netherlands

In the Netherlands no standard registration of birth weight or gestational age exists. The data presented here are derived from the Project On Preterm and Small for gestational age infants (POPS), a nationwide collaborative follow up study of very preterm (<32 completed weeks' gestation) and very low birthweight (weighing <1500 g at birth) infants born in 1983. Of 1338 infants enrolled in this study, 1097 (82%) weighed less than 1500 g at birth and 816 (74%) of these survived more than 28 days. Only minimal data were available on a further 67 infants weighing less than 1500 g and these were included only to calculate the incidence of very low birthweight infants.

Oxford region (UK)

The Oxford region is made up of four counties, Berkshire, Buckinghamshire, Northamptonshire, and Oxfordshire. In 1984-6 there were 806 infants with a birth weight of less than 1500 g who were registered as live born and were born to residents of the area. Of these, 605 (75%) survived more than 28 days.

INFORMATION ON DEATHS

The Netherlands

Information on deaths in hospital was obtained directly from the hospital of birth and

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information on deaths after discharge was collected at the time of follow up. As almost all families were contacted, deaths after discharge are unlikely to have been missed.

Oxford region (UK)

Copies of death certificates were obtained for all infants who were registered as live born and who died before the age of 5 years. Information on infants who died outside the region was conveyed to the district health authority of residence at the time of birth. The number of recorded deaths, apart from deaths among children who had emigrated, were considered to be complete.

INFORMATION ON HEALTH STATUS OF SURVIVORS

The Netherlands

At the age of 5 years 736 (96%) of 767 survivors with a birth weight less than 1500 g were assessed during home visits by one of three specially trained paediatricians using a standardised neurodevelopmental and sensory assessment. Details on assessment methods have been described elsewhere¹⁴; results on these assessments have also been reported elsewhere.¹⁵

Oxford region (UK)

Information on motor and sensory disability among surviving children was obtained from two sources. The Oxford region register of early childhood impairment provided information on all children with cerebral palsy, severe vision loss, or sensorineural deafness who were born to residents in the region.¹⁶ The register was set up in 1984 and uses multiple sources of ascertainment and relies on accurate and prompt reporting of cases by health personnel throughout the region.

A second source of ascertainment was available from a follow up study of infants with a birth weight less than 1000 g who were born in 1984–6. They were assessed at home at the age of 4 years by a paediatrician.

STANDARD RECORDING OF INFORMATION ON CEREBRAL PALSY

Cerebral palsy was defined as a non-progressive disturbance of movement or posture due to maldevelopment or damage of the immature brain. Major congenital anomalies affecting the central nervous system, degenerative

central nervous system diseases, and diseases acquired after the neonatal period were excluded.

The same standard form for describing children with cerebral palsy was used in the two studies.¹⁷ In the first part of this form the abnormalities in tone are described limb by limb, and the type of additional unwanted movements and the presence of bulbar signs are recorded. The severity of the child's disability is recorded in the second part of the form using a four point grading system to describe head control, trunk control, gait, and hand use. For the purposes of comparison in this study, grade 1 in this system was normal function, grade 2 was termed mild disability, grade 3 was moderate disability, and grade 4 was severe disability. The final section of the form describes associated impairments and disabilities, including vision loss, sensorineural deafness, and intellectual impairment.

STATISTICAL ANALYSIS

The relations between area of birth (Oxford region or the Netherlands) and birthweight group, neonatal mortality, rate of cerebral palsy, and severity of cerebral palsy were expressed as odds ratios (ORs) with 95% confidence intervals (95% CI). If the ORs were not significantly different (test on homogeneity), an average odds ratio was calculated using the Mantel-Haenszel procedure. A $p < 0.05$ was considered significant. Data were processed using EGRET.¹⁸

Results

INCIDENCE OF INFANTS WITH BIRTH WEIGHT <1000 g AND 1000–1500 g

There were 170 246 live births in the Netherlands in 1983 (Centraal Bureau voor Statistiek 1985) and 98 082 live births in 1984–6 in the Oxford region (UK). The reported incidence of live births of infants weighing less than 1000 g was higher in the Oxford region than in the Netherlands ($p < 0.001$) (table 1). In the 1000–1499 g group the incidence in the Oxford population was also higher, but the difference in the incidences was no more than would be expected by chance.

NEONATAL MORTALITY AND RATES OF CEREBRAL PALSY

The neonatal mortality was significantly lower in the Oxford population than in the Netherlands population among the infants weighing 1000–1499 g (OR 0.64; 95% CI 0.46 to 0.89; $p < 0.01$). Among infants weighing less than 1000 g the neonatal mortalities were similar (table 2).

In the two study populations the birth cohort prevalence of cerebral palsy was lower in the < 1000 g group than in the 1000–1499 g group. In the Netherlands population the ratio of the odds of cerebral palsy in the infants weighing 1000–1499 g to the odds of cerebral palsy in the infants weighing less than 1000 g was 1.95 (95% CI 1.1 to 3.45); in the Oxford

Table 1 Number and rate of live births by birthweight group. Values are number (rate/1000 live births)

	Netherlands (n=170 246)		Oxford (n=98 082)	p Value
Live births <1500 g	1164 (6.8)		806 (8.2)	
Difference in rates (95% CI)		1.4 (0.7 to 2.1)		<0.001
Live births 1000–1499 g	858 (5.04)		547 (5.58)	
Difference in rates (95% CI)		0.5 (0.0 to 1.1)		0.07
Live births <1000 g	306 (1.8)		259 (2.6)	
Difference in rates (95% CI)		0.8 (0.5 to 1.2)		<0.001

n=number of live births.

Table 2 Neonatal mortality and rates of cerebral palsy by birthweight group. Values are number (rate/1000 live births)

	<1500 g		1000–1499 g		<1000 g	
	Netherlands (n=1097)	Oxford (n=806)	Netherlands (n=805)	Oxford (n=547)	Netherlands (n=292)	Oxford (n=259)
Neonatal deaths	281 (256)	201 (249)	138 (171)	64 (117)	143 (490)	137 (529)
OR (95% CI)*	NA†		0.64‡ (0.46 to 0.89)		1.17 (0.83 to 1.66)	
Cerebral palsy	64 (58)	42 (52)	55 (68)	32 (59)	9 (31)	10 (39)
OR (95% CI)*	0.91 (0.60 to 1.39)		0.85 (0.53 to 1.36)		1.26 (0.47 to 3.44)	

n=No of live births.

* Odds ratio (OR): Oxford=numerator; Netherlands=denominator.

†Common estimate not applicable because ORs in the two birthweight categories are significantly different.

‡p<0.01.

Table 3 Severity of motor disability in cerebral palsy by birthweight group. Values are number (rate/1000 live births)

	<1500 g		1000–1499 g		<1000 g	
	Netherlands (n=64)	Oxford (n=42)	Netherlands (n=55)	Oxford (n=32)	Netherlands (n=9)	Oxford (n=10)
Not walking independently	28 (26)	26 (32)	26 (32)	21 (38)	2 (7)	5 (19)
OR (95% CI)*	1.28 (0.74 to 2.21)		1.20 (0.66 to 2.17)		2.69 (0.61 to 11.99)	
% Of those with cerebral palsy not walking independently	44	62	47	66	22	50
OR (95% CI)*	2.05† (0.95 to 4.46)		2.08 (0.87 to 4.95)		3.10 (0.50 to 19.07)	

n=No with cerebral palsy.

* Odds ratio (OR): Oxford=numerator; Netherlands=denominator.

†0.05<p<0.10.

population the OR was 1.5 (95% CI 0.77 to 2.91).

The rate of cerebral palsy in the Oxford population was higher than in the Netherlands population in the <1000 g group but lower in the 1000–1499 g group, but the differences were no more than would be expected by chance.

SEVERITY OF DISABILITY AMONG CHILDREN WITH CEREBRAL PALSY

We were concerned that differing methods of finding the children with cerebral palsy in the two populations could have obscured true differences in cerebral palsy rates. For example, in clinicians reporting children to the Oxford register, there could be differences in the inclusion and exclusion criteria used, particularly for children with mild cerebral palsy. We therefore used the four point grading of lower limb function on the standard reporting form to exclude the mild cases (grades 1 and 2) and then compared the prevalence of the more severe (grades 3 and 4) cases in the two populations (table 3). Numbers of subjects were small but now the cerebral palsy rate was higher in the Oxford population in the <1000 g group and in the 1000–1499 g group. The differences were, however, compatible with chance variation.

Co-morbidity (the presence of associated sensory or intellectual deficit, or both) was then used as a measure of severity of disability (table 4). In the Oxford population seven (17%) of the 42 children with cerebral palsy had an associated severe vision problem compared with five (8%) of the 64 children with cerebral palsy in the Netherlands population (table 4). Likewise, the proportion of children with a sensorineural hearing loss was higher in the Oxford population than in the Netherlands population, but the numbers of subjects were very small. Half of the children in the two populations were intellectually impaired: 23/42 in the Oxford group and 32/64 in the Netherlands group.

Discussion

Our attempts to compare mortality and rates of cerebral palsy in two populations of low birthweight infants highlighted a number of problems. These included problems arising from differences in the birthweight distribution, in the ways in which the surviving children were found and their health status described, and in the small number of cases of cerebral palsy in the study populations.

Table 4 Co-morbidity of cerebral palsy by birthweight group. Values given are number (rate/1000 live births)

	<1500 g		1000–1499 g		<1000 g	
	Netherlands (n=64)	Oxford (n=42)	Netherlands (n=55)	Oxford (n=32)	Netherlands (n=9)	Oxford (n=10)
Severe vision loss	5 (5)	7 (9)	5 (6)	5 (9)	0 (0)	2 (8)
OR (95% CI)*	1.93 (0.61 to 6.09)		1.49 (0.42 to 5.29)		8.43 (0.52 to 99.99)	
Sensorineural deafness	3 (3)	5 (6)	2 (2)	4 (7)	1 (3)	1 (4)
OR (95% CI)*	2.29 (0.56 to 9.33)		2.98 (0.58 to 15.26)		1.13 (0.07 to 18.17)	
Intellectual impairment	32 (29)	23 (29)	28 (35)	19 (35)	4 (14)	4 (16)
OR (95% CI)*	0.98 (0.57 to 1.68)		1.00 (0.55 to 1.81)		1.13 (0.28 to 4.57)	

n=No with cerebral palsy.

* OR: Oxford=numerator; Netherlands=denominator.

FACTORS INFLUENCING BIRTHWEIGHT DISTRIBUTION

The two populations we studied had a number of similarities. They were both large cohorts defined by residence at the time of birth, hence avoiding the selection bias inevitable in hospital based comparisons, they were born in similar but not identical time periods, and the weight limits used to define the populations were the same.

The weight distribution of the populations differed, however, and there was a higher proportion of liveborn infants weighing less than 1000 g in the Oxford population. This could have been due to a number of reasons such as differing socioeconomic factors and ethnic composition of the populations,^{19 20} or a difference in the number of multiple pregnancies, perhaps as a result of differing approaches to newer techniques of assisted reproduction.²¹ Alternatively, there may have been differences in obstetric practice,²² which might have influenced the ratio between liveborn infants and abortions or stillborn fetuses, for example, by intensive management of the high risk very preterm fetus. Similarly, differing perceptions of the chance of survival for the very preterm infant may have resulted in differences in the reporting of live births at early gestational ages, particularly as deaths of fetuses born before 28 weeks' gestation were not registered as stillbirths at that time, either in England or in the Netherlands.²³ There is evidence from birth registration data in the UK that the proportion of live births of infants weighing less than 1000 g has been increasing through the 1980s,² presumably reflecting the increased optimism about the chances of intact survival and a changing interpretation among clinicians of the criteria for defining registrable live births.

Differences in defining registrable live births occur particularly among infants at the borderline of viability and such registration differences could be expected to result in differing mortalities. The Oxford population had a higher incidence of liveborn infants weighing less than 1000 g but the neonatal mortality in this group did not differ from the Netherlands population. This observation, together with the lower neonatal mortality in the 1000–1499 g group in the Oxford population, suggests that registration differences do not entirely account for the differences in weight distribution.

POSSIBLE EFFECTS OF DIFFERENCES IN APPROACH TO NEONATAL INTENSIVE CARE ON MORTALITY IN EXTREMELY LOW BIRTHWEIGHT INFANTS

It is possible that a different approach to the option of withholding or withdrawing treatment could contribute to the mortality differences.^{24–26} Decisions not to start treatment or to withdraw treatment accounted for over half of the neonatal deaths in the Netherlands study population²⁷ and for about one third in the Oxford population. Variations in this policy will inevitably have an effect on mortality.

Decisions on withholding or withdrawing treatment may be determined to some extent

by the presence of haemorrhagic and ischaemic changes in the brain. As such lesions among survivors are known to be predictive of later neurodevelopmental impairment, a higher rate of cerebral palsy might be expected to occur in the population with a lower neonatal mortality.

We found no clear differences in the rates of cerebral palsy in the two populations in either of the two birthweight groups. There are at least three possible reasons for this. Firstly, the inverse relation between neonatal mortality and cerebral palsy does not exist, perhaps because the aetiological factors underlying cerebral palsy may differ from the factors which determine neonatal death. The existing epidemiological and neuropathological evidence suggests that this is unlikely. Secondly, though the two study populations were large, the numbers of cases of cerebral palsy are too small to show differences. Pooling and comparison of large data sets will help to clarify this issue. The third possibility is that the different methods of ascertaining the cases of cerebral palsy have obscured a true difference in the rate of cerebral palsy.

EFFECT OF DIFFERENCES IN CASE ASCERTAINMENT

Differences in methods of finding and describing children could result in a serious bias when comparing rates of cerebral palsy in two populations. In our study there was a number of similarities in the two methods for ascertainment of the children with cerebral palsy. Firstly, the age of assessment was similar. This is important because a general shift in severity from more severe to milder motor disorders has been described to occur with increasing age.^{28–31} Secondly, the method of case finding for children with a birth weight <1000 g was similar (assessment at home by a paediatrician using a similar protocol). No active follow up was performed in the 1000–1499 g group in the Oxford study, however, so it is possible that children with milder motor disorder could have been missed by the passive reporting system used by the Oxford register. Use of the severity grading system in the standard form helped to clarify this issue.

To our knowledge, this is the first time that the standard descriptive form, which was designed particularly for use in epidemiological studies, has been used to compare two populations of children with cerebral palsy. In the past, differences in terminology of cerebral palsy,³² in allocating levels of severity to the disability, and interobserver differences in the description of the clinical findings have led to difficulties in describing children with cerebral palsy. The standard form addresses all these problems; all jargon terms are excluded and a descriptive limb by limb approach is used. The categorisation of children with similar functional severity was particularly useful in clarifying the effect of the differing methods of case finding on rates of cerebral palsy. By defining a critical threshold of severity above which all cases are expected to come to the attention of

clinicians or institutions, this effect became less important.

In summary, despite efforts to control for known biases, the comparison of mortality in different populations of low birthweight infants proved difficult. In particular, the effect of possible differences in the registration of very preterm infants and differences in the policies in withholding and withdrawing treatment could not be controlled for.

Differences in registration practice would be reduced if the criteria for registration of live birth and stillbirth were brought into line with World Health Organisation definitions. In this way all infants weighing >500 g would be registered and the denominators would be clearer.

Since the mid 1980s when these two cohorts were born, the perceptions of the chance of survival of the smallest infants have no doubt changed and the threshold for withholding or withdrawing treatment will also have changed. These will, however, probably remain as options when decisions are taken after the birth of an extremely immature infant and will have an effect on neonatal mortality and on rates of cerebral palsy.

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