

Comparison of risk factors for cerebral palsy in twins and singletons

S R Bonellie, BSc, MSc, PhD, Lecturer, Centre for Mathematics and Statistics,
Napier University, Edinburgh

D Currie, BSc, MSc, Senior Research Fellow, Child and Adolescent Health Research
Unit, Department of PESLS, The University of Edinburgh

J Chalmers, MBChB MSc MRCGP FFPH, Consultant in Public Health Medicine,
Information and Statistics Division, NHS Scotland

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Address for correspondence

S R Bonellie
Centre for Mathematics and Statistics
Napier University
10 Colinton Road
Edinburgh
EH10 5DT

Fax: 0131 455 2651

e-mail: s.bonellie@napier.ac.uk

Aim: To investigate differences between rates of cerebral palsy in singletons and twins by considering factors that may be predictive of cerebral palsy.

Methods: Data from the Scottish Register of Children with a Motor Deficit of Central Origin and routinely collected maternity data from the Scottish Morbidity Record series (SMR2) was used. All children born between 1984 and 1990 inclusive comprise the cohort. Cerebral palsy prevalence was calculated as cases registered per thousand neonatal survivors. Logistic regression was used to obtain odds ratios for the risk of cerebral palsy.

Results: There were 646 cerebral palsy cases of which 57 were from twin pregnancies. The cerebral palsy prevalence was higher in twins than in singletons. Also, for both singleton and twin births, the prevalence was higher for low birthweight- for-gestational age, preterm birth and for males. However, the cerebral palsy prevalence by gestational age followed a different pattern for twins than for singletons being lower for twins in the middle range of gestational ages than for singletons.

Conclusions: After allowing for gestational age and birthweight, twins are at increased risk of CP compared to singletons. The aetiology of CP in twins and singletons may differ.

Running title: Risk factors for CP

Previous studies have found the prevalence of cerebral palsy (CP) to be greater in multiple than in singleton pregnancies (Pettersson, Nelson, et al.,1993;Pharoah and Cooke,1996;Pharoah, Price, et al.,2002) The aim of this study is to examine possible differences in risk factors for CP in singleton and twin births. Factors unique to twin births, such as the outcome of the co-twin, will also be examined.

Method

The Scottish register was established by the Public Health Research Unit in Glasgow in 1990 and contains information on cases of children with a motor deficit of central origin born from 1984 onwards (Mutch and Ronald,1992). The cases were sought from multiple sources, including the health service, education authorities, voluntary agencies and death certification. Record linkage was used to connect the register to information on all births in Scotland using the maternity part of the Scottish Morbidity Record series (SMR2). Permission to link to medical records was obtained from the parents/carers when the child was entered onto the register and the Privacy Advisory Committee gave approval for the study. Linkage was carried out on a 'one-pass' best-link basis (Kendrick and Clarke,1993), whereby each CP record was allowed to make a best possible match to a corresponding SMR2 record.

The purpose of the linkage was three-fold. Firstly, and most importantly, it gave access to denominator data on perinatal risk factors to allow a retrospective cohort study of births. In calculating CP prevalence, stillbirths and neonatal deaths have been excluded from the denominator. The rates given are therefore the recorded rates of registered cases of CP per thousand neonatal survivors.

The linkage also gave additional information about the birth that is not included on the register in particular information about the co-twin in cases of twin pregnancies. Finally it enabled a check on the accuracy of the information to be carried out. Information on birthweight and gestational age is common to both data sources. Where a discrepancy was found, it was assumed that the SMR2 record was more reliable since the data on the register relies on the mother's recall.

A diagnosis of CP made before the age of two may be unreliable and therefore it may take time before all cases in a birth cohort can be identified. Furthermore, the diligence of the multiple source ascertainment process was greatest in the earlier years of the register. For these reasons the following analyses use data from births occurring between the years of 1984 to 1990 only. It is probable that not all cases of CP are included on the register and the number of actual cases may be higher than the number registered. However the missing cases are probably geographically determined in that some Health Boards were better at returning data than others.

Those identified as having CP acquired post-neonatally, cases with a specific syndrome e.g. Rett's syndrome of which CP is a recognised manifestation, those who were diagnosed before 2 years of age where the diagnosis had not been confirmed subsequently and those children whose mothers were not resident in Scotland at the time of the birth were omitted from the analysis. Cases where the diagnosis of CP was only obtained from a death certificate were also omitted.

The effect of the birthweight of the infant on the rate of CP was investigated in five categories: < 1000, 1000 - 1499, 1500 -1999, 2000 -2499 and \geq 2500 grams.

Gestational age was divided into four categories: 24-27, 28-31, 32-36 and \geq 37 weeks.

Birthweight and gestational age are highly correlated and, comparison of twins and singletons by birthweight alone may not be appropriate. Twins tend to be born earlier than singletons and have lower birthweights. A more appropriate approach is to compare twins and singletons by the expected birthweights for gestational age, using the population based data. Birthweights for each gestational age were divided into 5 equal groups and classified as coming from the 1st, 2nd, 3rd, 4th or 5th quintile of weight for gestational age.

Since differences in recorded birthweight and gestational age between SMR2 and the register were found to be minor and too small to effect the conclusions, the calculation of prevalence and odds ratios of CP for birthweight and gestational age based on both the cases that linked to the SMR2 data and the cases for which no link was established. Rates of CP and odds ratios for different factors were calculated for singletons and for twins separately. Logistic regression models were fitted to the data to compare the risk factors for twins and singletons.

The linkage also gave information on the co-twin which allowed the effect of factors such as the outcome for the other twin and discordancy in birthweight to be studied. To investigate the difference between monozygotic and dizygotic twins Weinberg's method (Weinberg, 1901) was used to estimate the number of monozygotic twins. Confidence intervals for the corresponding odds ratios were calculated to allow for numbers of monozygotic and dizygotic twins being estimates. These calculations omit those cases for which no link was established.

Results

The data were from the years 1984-1990 and comprised 442,662 live singleton births and 9248 live twin births from 4749 twin pregnancies with at least one surviving child. Comparison with the General Register Office for Scotland (GRO(S)) registration data indicates that the SMR2 data set is more than 98% complete, although it is known that recording of home deliveries (of which there are few) is less complete.

There were 836 cases of CP on the register born 1984-1990. Of these 646 were included in the analysis comprising 586 singletons, 57 twins and 3 triplets. Table 1 summarises those cases that were not be included.

Of the 646 cases from the register 570 (88.2%) were successfully linked to the delivery records. No significant differences between the two groups were found with respect to the variables used in this analysis. Of the 57 twins on the register a link was found for all but five.

From the Scottish register from 1984 to 1990, the CP prevalence per thousand neonatal survivors for singletons is 1.32, (95% CI: 1.22, 1.44), and for twins is 6.39, (95% CI: 4.97, 8.22). The odds ratio in twins compared to singletons is 4.83, (95% CI: 3.80,6.13). The number of children with each type of CP for twins and singletons is shown in Table 2.

Information on co-twin

There were three sets of twins where both children have CP of which two sets were like-sex. Of the 51 twin pairs with one child affected, 26 were first-born. Where one twin was either stillborn or died neonatally the odds ratio of the co-twin having CP compared to cases where both twins survive is 6.3, (95% CI: 3.1,12.8).

Discordance in birthweight was measured by expressing the absolute difference in the birthweight of the two twins as a proportion of the maximum birthweight. This was calculated only for those cases where both twins were neonatal survivors. For twins where at least one infant was diagnosed with CP the mean level of discordancy was 14.2% compared to 11.3% for those where neither twin had CP. Table 3 shows the rate of CP increasing as the level of discordancy in birthweights increases. A Mantel-Haenszel test for trend was highly significant. For each of the discordancy groups about half of the children with CP were the lightest child at birth.

Information on the zygosity of the twins was not available however the sex of both twins was known. 71.2% of the twins born in this period were of like sex. For CP cases this rose to 81.6%. The odds ratio for like-sex twins to unlike-sex twins cases is 1.79 (95% CI: 0.87, 3.71). Using Weinberg's method the odds ratio for CP in monozygotic twins compared to dizygotic twins is 2.33, (95% CI: 0.91, 5.96).

Comparing twins and singletons

The odds ratios for twins compared to singletons together with 95% confidence intervals by birthweight and gestational age categories are given in Table 4. Gestational age was missing for 0.7% of the singleton births and for 0.4% of the twin pairs. Of those records with missing gestational ages, 8 singletons and 1 twin had CP.

The rates and odds ratios for birthweight-for-gestational age were then calculated for each group and are also shown in Table 4 together with confidence intervals. For twins and singletons the only significant difference in prevalence occurs between the first quintile of birthweight-for-gestational age and the rest, with the rate of CP being highest in this group. The difference between twins and singletons is illustrated in Figure 1

which shows, on a log scale, the rates by gestational age for twins and singletons for those in the lowest quintile of birthweight-for-gestational age.

Further analysis was carried out using only two categories for relative birthweight for gestational age, those in the lower twenty percent of birthweight for gestational age compared to those above.

The results from fitting logistic models to the data are summarised in Table 5. For singletons the data set consisted of a total of 439316 observations of which 575 had CP. There were 9241 twins with 55 CP cases. The unadjusted and adjusted odds ratios for CP by birthweight, gestational age and sex are given for both singletons and twins. The base categories are higher relative birthweights for gestational age, gestational ages of 37 weeks or more and female infants.

Discussion

This study successfully used record linkage to demonstrate and quantify the excess risk of CP experienced by twins compared to singletons which is not explained by low birthweight or prematurity. A recurring problem in the analysis of CP data is the lack of reliable denominator data. In particular many previous studies have been restricted to either preterm or term infants because of lack of access to data on gestational age (Murphy, Hope, et al.,1997;Topp, LanghoffRoos, et al.,1997). A recent paper on CP in twins (Pharoah, Price, et al.,2002) examined differences in rates of CP by birthweight but not by gestational age. The ability to link the data from the CP register with data from the SMR2 forms gives access to both good denominator data and to reliable information on gestational age as well as birthweight and to other information not contained on the register.

The success rate achieved in the data linkage is lower than usual for this type of exercise and is probably explained by the fact that the linkage is between the records of the child and the record of the mother. The rates given here are based on the number of registered cases of CP, which will be lower than the true rates. Since the reason for cases being missing is largely geographical there is no reason to suppose that the lower observed rates occur any more frequently in twins than in singletons.

Almost 65% of the twins were recorded as having spastic bilateral CP compared to less than 50% for singletons. There is evidence that different types of CP have a different aetiology (Pharoah, Platt, et al., 1996; Pharoah, Cooke, et al., 1998) In particular it has been suggested that the risk of spastic bilateral CP is higher at low birthweights than the risk of spastic hemiplegia which is found more in infants weighing over 2500 grams. In the singleton population only about 5% of the infants weigh less than 2500 grams at birth. This compares to over 50% for the twin population, while for the twins with CP 84% have birthweights below 2500 grams.

Information on the co-twin

There is no evidence from these data to suggest that birth order has any effect on the risk of CP since approximately half of the children with CP were the first born. There is however clear evidence that the risk of CP is affected by the outcome of the co-twin.

Where the co-twin dies neonatally or is stillborn, the risk of the surviving twin having CP is significantly higher than when both twins survive.

These results also suggest that where there is a high level of discordancy in birthweight the risk of CP is increased. Although the risk of CP was related to the degree of discordancy there was no pattern to which child, the lighter or heavier, was affected.

Previous studies on discordancy, (Cheung, Bocking, et al.,1995) also found increased risk of adverse perinatal outcomes in twin pairs with high levels of discordancy. The study concluded that there was an increased risk of neonatal death for the lighter of the two children when the level of discordancy was over 30% but there was no clear pattern of an increased risk for the lighter child for other adverse outcomes.

Other studies have suggested that there is an increased risk of CP among monozygotic as opposed to dizygotic twins. The comparative rates in like and unlike sex twins, showed an increased risk among like sex twins but the difference was not significant, possibly because of the small number of cases. It has been previously been reported (West, Adi, et al.,1999) that survival rates are lower in monozygotic twins compared to dizygotic twins and this may reduce the number of cases of CP observed in monozygotic twins. The increased risk for monozygotic twins is suggested for these data when the numbers of twin pairs of each type are estimated using Weinberg's method. However, the estimates of the numbers of monozygotic and dizygotic twins with CP must be treated with caution.

These estimates are based on the assumption that the sex ratio is 1:1. However these data show that there is an increased risk of CP in male babies. A sensitivity analysis was carried out in which the number of monozygotic and dizygotic twins was estimated using the observed sex ratio and it was found that this made practically no difference to the odds ratio or its confidence interval.

Comparing rates in twins and singletons

For both singletons and twins the rate of CP is considerably higher among babies born at earlier gestational ages compared to those born nearer to term. It is only at the highest

gestational age that a significant difference between the two is observed with twins having a much higher rate than singletons. It is notable that the rates for twins are lower than the rates for singletons in the middle gestational ages. In contrast, for weights greater than 2500, the rate for twins is almost 3 times the rate for singletons.

Survival rates in preterm multiple births is, for the same birthweight and gestational age, are higher than for singletons (Draper, Manktelow, et al., 1999). Birth at an early gestation is more frequent for a twin pregnancy than a singleton pregnancy. This may indicate that factors precipitating the early delivery, rather than the early delivery and small birthweight themselves which are important in the pathogenesis of CP in singletons at early gestation.

Overall the rates for twins vary less with birthweight and gestational age than the rates for singletons and therefore the observed higher risk of CP among twins cannot simply be attributed to their lower birthweights and earlier gestational ages. Being a twin in itself increases the risk of CP.

Logistic regression was used to study the combined effect of factors. The results suggest that both birthweight and gestational age are important predictors of CP. Of course babies with a low gestational age are also likely to be the babies with low birthweight.

It can be argued that like is not being compared with like since twin infants are born earlier and weigh less than singletons on average. Looking at the results for birthweight-for-gestational age in quintiles, the univariate analysis shows that the risk of CP in twins is consistently about 4-5 times higher than the risk for singletons. These results certainly suggest that the observed difference between twins and singletons are not simply due to the obvious differences in birthweight and gestational age.

In conclusion, for both singleton and twin births birthweight, gestational age and sex of

the infant are all predictive of the prevalence of CP. However the pattern of cases differs substantially between twins and singletons and the higher rate of CP in twins cannot be solely attributed to their lower birthweight and gestational age.

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| Status | Number | Percentage |
|------------------------------------------|---------------|-------------------|
| Syndrome of which CP is a manifestation | 73 | 8.7 |
| Post-neonatal CP | 31 | 3.7 |
| CP diagnosis not confirmed | 27 | 3.2 |
| CP diagnosis from death certificate only | 54 | 6.5 |
| Birth outwith Scotland | 5 | 0.5 |
| Total | 118 | 14.1 |

Table 1

| Type of cerebral palsy | Twins | | Singletons | |
|------------------------|--------|------------|------------|------------|
| | Number | Percentage | Number | Percentage |
| Spastic bilateral | 37 | 64.9% | 284 | 48.5% |
| Spastic hemiplegic | 13 | 22.8% | 153 | 26.1% |
| Dyskinetic | 4 | 7.0% | 85 | 14.5% |
| Ataxic | 1 | 1.8% | 36 | 6.1% |
| Not known | 2 | 3.5% | 28 | 4.8% |

Table 2

| | Discordancy | | |
|----------------------|----------------------------------------------|--------------------------|------------------------------------------------|
| | Number Registered with Cerebral Palsy | Rate per thousand | Odds ratio with 95% confidence interval |
| Less than 10% | 16 | 6.77 | 1.00 (base) |
| 10% - 30% | 19 | 9.80 | 1.45 (0.75,2.83) |
| More than 30% | 7 | 35.0 | 5.17 (2.16,130.8) |

Table 3

| | Registered cases of cerebral palsy | | Rates per 1000 neonatal survivors | | Odds ratio of cerebral palsy in twins compared to singletons | |
|-----------------------------------------------------|-----------------------------------------------|--------------|----------------------------------------------|--------------|-----------------------------------------------------------------------------|-----------------|
| Weight, grams | Singletons | Twins | Singletons | Twins | Odds ratio | 95% c.i. |
| <1000 | 28 | 12 | 34.4 | 85.7 | 2.63 | 1.30-5.31 |
| 1000-1499 | 87 | 11 | 46.2 | 21.8 | 0.46 | 0.24-0.87 |
| 1500-1999 | 97 | 15 | 21.7 | 12.4 | 0.57 | 0.33-0.98 |
| 2000-2499 | 80 | 10 | 4.8 | 3.4 | 0.71 | 0.37-1.37 |
| ≥ 2500 | 294 | 9 | 0.7 | 2.0 | 2.85 | 1.47-5.54 |
| Gestational age, weeks | | | | | | |
| 24-27 | 32 | 10 | 63.5 | 87.0 | 1.40 | 0.67-2.95 |
| 28-31 | 111 | 15 | 47.0 | 27.9 | 0.58 | 0.34-1.01 |
| 32-36 | 118 | 20 | 5.9 | 6.0 | 1.02 | 0.63-1.63 |
| 37 and over | 317 | 11 | 0.8 | 2.1 | 2.74 | 1.50-5.01 |
| Relative birthweight for gestational age | | | | | | |
| 1st quintile | 170 | 18 | 1.9 | 9.7 | 5.09 | 3.13-8.30 |
| 2nd quintile | 105 | 12 | 1.2 | 6.5 | 5.46 | 3.00-9.95 |
| 3rd quintile | 103 | 10 | 1.2 | 5.4 | 4.68 | 2.44-8.97 |
| 4th quintile | 103 | 9 | 1.2 | 4.8 | 4.14 | 2.09-8.20 |
| 5th quintile | 94 | 7 | 1.1 | 3.8 | 3.58 | 1.66-7.73 |

Table 4

| Parameter | Singletons | | | Twins | | |
|-------------------------------------------------|------------|---------------------|-------------------|------------|---------------------|-------------------|
| | Odds ratio | Adjusted odds ratio | Confidence limits | Odds ratio | Adjusted odds ratio | Confidence limits |
| Gestational age | | | | | | |
| 24-27 | 91.22 | 93.56 | 64.26-136.2 | 47.25 | 49.25 | 20.37-119.1 |
| 28-31 | 64.91 | 64.45 | 51.65-80.41 | 13.79 | 13.62 | 6.21-30.06 |
| 32-36 | 7.75 | 7.69 | 6.21-9.51 | 2.73 | 2.72 | 1.29-5.73 |
| ≥37 | 1.00 | 1.00 | | 1.00 | 1.00 | |
| Relative birthweight for gestational age | | | | | | |
| Lowest quintile | 1.68 | 1.75 | 1.46-2.10 | 1.81 | 1.94 | 1.08-3.50 |
| Upper quintiles | 1.00 | 1.00 | | 1.00 | 1.00 | |
| Sex | | | | | | |
| Male | 1.27 | 1.30 | 1.10-1.54 | 1.23 | 1.31 | 0.76-2.27 |
| Female | 1.00 | 1.00 | | 1.00 | 1.00 | |

Table 5

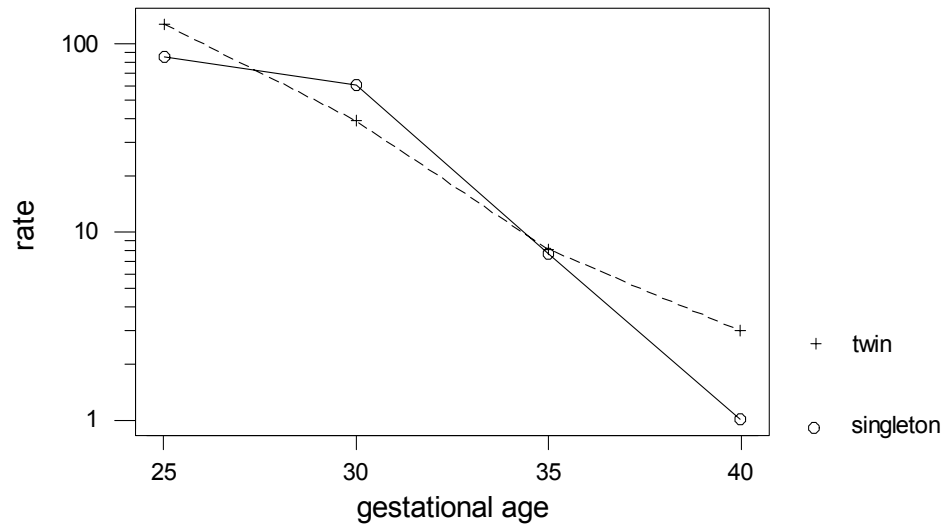


Figure 1

Table 1: Number and percentage of registered cases omitted from the analysis

Table 2: Types of cerebral palsy for singletons and for twins

Table 3: Discordancy in birthweights

Table 4: Rates of recorded cerebral palsy per 1000 neonatal survivors by birthweight, gestational age and relative birthweight for gestational age.

Table 5: Odds ratios for cerebral palsy by relative birthweight for gestational age, gestational age and sex.

Figure 1: Log of cerebral palsy rate per thousand neonatal survivors by gestational age for singletons and twins for the lower quintile of relative birthweight for gestational age.