A cohort study of low Apgar scores and cognitive outcomes

D E Odd,¹ F Rasmussen,² D Gunnell,³ G Lewis,⁴ A Whitelaw⁴

ABSTRACT

Objective: To investigate the association of brief (0–5 minutes) and prolonged (>5 minutes) low Apgar scores (<7) in non-encephalopathic infants with educational achievement at age 15–16 and intelligence quotients (IQs) at age 18.

Design: Population-based record-linkage cohort study of 176 524 male infants born throughout Sweden between 1973 and 1976.

Patients and methods: Data from the Medical Birth Register were linked to Population and Housing Censuses, conscription medical records (IQ), and school registers (summary school grade). Infants were classified according to the time for their Apgar score to reach 7 or above. Premature infants and those with encephalopathy were excluded.

Results: Infants with brief (OR = 1.14 (1.03–1.27)) or prolonged (OR = 1.35 (1.07–1.69)) low Apgar scores were more likely to have a low IQ score. There was an increased risk of a low IQ score (p = 0.003) the longer it took the infant to achieve a normal Apgar score. There was no association between brief (OR = 0.96 (0.87–1.06)) or prolonged (OR = 1.01 (0.81–1.26)) low Apgar scores and a low summary school grade at age 15–16, or evidence for a trend in the risk of a low school grade (p = 0.61). The estimated proportion with an IQ score below 81 due to transiently low Apgar scores was only 0.7%.

Conclusions: Infants in poor condition at birth have increased risk of poor functioning in cognitive tests in later life. This supports the idea of a “continuum of reproductive casualty”, although the small individual effect suggests that these mild degrees of fetal compromise are not of clinical importance.

A severely low Apgar score at 5 minutes is strongly associated with an increased risk of neonatal encephalopathy, subsequent cerebral palsy (CP) and learning difficulties,¹ ³ although a low score may be due to conditions other than brain injury or intrapartum events. The current consensus is that clinically important brain damage leading to CP, with or without learning disability, can occur only if the hypoxic insult is significant enough to produce clinical encephalopathy in the neonatal period.¹ ⁵

The long-term outcome of infants with low Apgar scores who do not develop encephalopathy is considered to be normal with respect to CP,³ although infants with moderate neonatal encephalopathy who do not develop CP may develop some degree of cognitive impairment as teenagers.⁵ However, there is a lack of evidence as to whether infants with low Apgar scores without encephalopathy have subtle changes in brain function and reduced cognitive function later in life. It has been postulated that a “continuum of reproductive casualty” exists⁶—while profound perinatal events cause death or obvious neurological deficit, milder insults may cause subtle defects in functioning only detectable as the child grows older.

This study aimed at determining whether low Apgar scores in term newborn infants without encephalopathy are associated with measures of cognitive function and education attainment in adolescence and early adulthood.

METHODS

Linkages of Swedish datasets

The dataset is based on the birth registry records of male infants born in Sweden between 1973 and 1976, providing data on 98–99% of births.⁷ This registry was linked to the Population and Housing Census of 1970 and 1990 supplying socioeconomic data on their parents. Linkage to the Military Service Conscription data and Statistics Sweden’s register on school grade provided educational measures at 15–16 years and cognitive measures at 18 years old. This study was conducted as part of a longstanding collaboration between Bristol University, UK and the Karolinska Institute, Sweden.

Measures of cognitive and educational performance

The Swedish military and civil service conscription examination involves an assessment of cognitive function (the Swedish Enlistment Battery (SEB)). This examination was required by law, with only men of foreign citizenship or those with a severe medical condition or disability excused.⁸ During the SEB, intelligence quotient (IQ) was measured by four subtests representing logical, spatial, verbal and technical abilities. All test scores, including global IQ (a summation of the subtests), were standardised to give a Gaussian distributed score between 1 and 9. All children in Sweden have a summary school grade calculated at the age of 15–16 years. This grade is made up of all subjects taken and is scored between 1 and 5. Higher values indicate greater performance.

We created indicator variables for a poor performance in the SEB; with a score of 1–2 categorised as a low score (approximately the lowest 9% of scores). Poor performance in the school grade was defined as a score in the lowest 10%.

Measure of condition at birth

The Swedish Birth Registry records the Apgar scores measured at 1 and 5 minutes after birth.
Infants were classified depending on the time for their Apgar score to reach 7 or above (a normal score):
- A normal score by 1 minute of age (reference)
- A normal score by 5 minutes (briefly low)
- A score of <7 at 5 minutes (prolonged low).

Potential confounders or modifying variables
In addition, other risk factors were included in the analyses as potential confounders, split into three groups. Factors identified with an asterisk were extracted from maternal or infant diagnoses coded in the birth register, as appropriate:
- Antenatal
  - maternal parity
  - birth weight, length and head circumference (standardised for gestational age, and categorised into five groups based on the number of standard deviations (SD) their values were above or below the mean)
  - pre-eclampsia*
- Intrapartum/neonatal
  - mode of delivery (caesarean section, instrumental (vacuum extraction or forceps) or unassisted vaginal delivery)
  - maternal and neonatal infection*
  - season and year of birth
- Social factors
  - parental age at the time of the subject’s birth (<20 years, 20–24 years, 25–29 years and >29 years)
  - parental occupation (manual, non-manual, self-employed or other (including unemployed and students) and parental education (<9 years, 9–10 years, full secondary or higher education). Data from the 1990 census were used where possible, or where this was unavailable, the 1970 data were used.

Inclusion criteria
The dataset contained information on 212 606 male infants. Infants from multiple births (n = 5428), born before 37 weeks’ completed gestation (n = 11 155) or diagnosed with cardiovascular, respiratory, neurological or multiple system congenital abnormalities (n = 1613) were removed. Infants with a neonatal diagnosis of seizures, encephalopathy or brain injury (asphyxial or unknown cause) were excluded from the analysis (n = 2510 (1.1%)). Two hundred and four of these infants had a diagnosis of encephalopathy or seizures. The others were diagnosed with “asphyxia” or “anoxia” and were removed to ensure we excluded all infants with contemporaneous concern of a clinically important ischaemic insult. People who emigrated or died before conscription (n = 8709) were removed. This left 185 391 eligible subjects for the study. Birth weights, lengths or head circumferences more than 5 SDs from the mean (corrected for gestational age) were considered improbable entries and were removed (n = 1894). Infants with insufficient data to measured. In particular, they weighed less (3522 g vs 3608 g) and were more likely to have brief (4.54% vs 3.15%) or prolonged (0.95% vs 0.57%) low Apgar scores. Owing to the large sample size, all comparisons were significant (p<0.001).

Table 1 shows the distribution of the risk factors in the eligible infants. Owing to the introduction of a revised examination, the proportion of infants with appropriate SEB information decreased with the year of conscription (31 238 (91.3%) in 1991 vs 22 743 (58.7%) in 1994, p<0.001). School grade data were missing in 9407 (5.4%) subjects.

A total of 169 880 (96.2%) infants had achieved a normal (≥7) Apgar score by 1 minute, 5611 (3.2%) infants had achieved it by 5 minutes and 1033 (0.6%) still had a score of <7 at this point.

There was little evidence that the strength of association between Apgar scores and IQ scores differed according to parental occupation (mother p = 0.75, father p = 0.94), parental education (mother p = 0.68, father p = 0.48) or birth weight (p = 0.47).

Linear regression results are presented as the mean difference in SD/z-scores for that measure (table 2). In the fully adjusted models, infants with briefly low Apgar scores had lower logic (0.034 (0.005 to 0.063)), technical (0.052 (0.022 to 0.083)) and IQ (0.038 (0.005 to 0.061)) scores, but not lower synonym (0.011 (-0.015 to 0.038)) or spatial (−0.007 (−0.037 to 0.024)) scores. Infants with prolonged low Apgar scores also had lower logic (0.092 (0.025 to 0.158), spatial (0.091 (0.021 to 0.161), technical (0.071 (0.001 to 0.140)) and IQ (0.081 (0.017 to 0.145)) scores, but not lower synonym (0.036 (−0.025 to 0.097)) scores. There was no association between briefly low Apgar scores and school grade (0.010 (−0.015 to 0.034)), although infants with prolonged low Apgar scores had lower school grades (0.109 (0.085 to 0.166)).

In the fully adjusted logistic regression model (table 3) infants with briefly low Apgar scores were more likely to have low logic (OR = 1.25 (1.10 to 1.44)), technical (OR = 1.18 (1.04 to 1.35)) and IQ (OR = 1.14 (1.08 to 1.27)) scores, but not low synonym (OR = 1.09 (0.96 to 1.25)) or spatial (OR = 1.02 (0.90 to 1.16)) scores. Infants with prolonged low Apgar scores were more.
likely to have low logic (OR = 1.34 (1.01 to 1.78)), spatial (OR = 1.37 (1.05 to 1.77)) and IQ (OR = 1.35 (1.07 to 1.69)) scores, but not low synonym (OR = 1.26 (0.98 to 1.67)) or technical (OR = 1.03 (0.77 to 1.39)) scores.

There was no association between briefly OR = 0.96 (0.87 to 1.06) or prolonged OR = 1.01 (0.82 to 1.26) low Apgar scores and a low school grade.

Tests for trend indicated there was an increased risk of a low score in logic (p < 0.001), synonym (p = 0.04), technical (p = 0.04) and IQ scores (p = 0.005) the longer it took the infant to achieve a normal Apgar score. There was no strong evidence for a trend in the risk of a low spatial (p = 0.08) or school grade score (p = 0.61).

The proportion of people with a low IQ scores attributable to a briefly low Apgar scores was 0.50% (0.05 to 1.01%) and a prolonged low Apgar score 0.21% (0.01% to 0.19%). Repeating the analysis with a cut point of ≥4 for the Apgar scores produced similar results, although owing to the smaller number of infants in the exposure groups the CI were wider (eg, OR for low IQ; briefly low Apgar, 1.21 (0.97 to 1.50); prolonged low Apgar, OR = 1.33 (0.72 to 2.45); test for trend p = 0.06). There was an increased risk of low IQ scores (OR = 3.51 (1.89 to 5.78)) in the 82/204 infants with encephalopathy who survived and had SEB data available.

**DISCUSSION**

**Principal findings**

We found an association between poor condition at birth and long-term cognitive functioning in term infants without apparent neonatal encephalopathy. Infants with prolonged, or even brief, low Apgar scores but without neurological signs seemed to have a higher risk of poor IQ scores at age 18 years. Given the limited effect on mean scores, and modest association with “poor” scores, the effects seen are probably of limited clinical significance for individual infants. In context, infants with encephalopathy had a substantially increased risk of a low IQ (OR = 3.31 (1.89 to 5.78)) score.

**Study design**

This was a large study, with relatively few missing data, and an opportunity to control for several important confounders such as socioeconomic position and birth weight, although any interpretation may be limited to male infants only. Around 2–3% of men are exempt from the SEB examination owing to medical conditions but this should not have affected our ability to investigate the hypothesis. The higher proportion of subjects with missing data in the later years was due to administrative changes and is unlikely to have biased any results. Although the Apgar score is dependent on factors other than hypoxia, it has been shown to be strongly associated with other measures of asphyxia. In addition, many other causes of a low Apgar score have been controlled for (eg, premature, congenital abnormalities, sepsis, etc.) or are rare (eg, neuromuscular disorders).

This study aimed at investigating the association in term infants without encephalopathy, and 2310 infants were excluded because of possible clinical concerns. Two hundred and four (1.0/1000) term infants had a diagnosis of encephalopathy or seizures, a prevalence similar to that reported elsewhere. Analyses repeated including these infants produced similar results (data not presented). We chose not to use Bonferroni corrections to adjust our p values for the associations with the six different cognitive end points we investigated. Scores for the measures of cognitive function were strongly intercorrelated (correlations coefficients between 0.55 and 0.85), and so such an approach would be overly conservative.

**Possible mechanisms**

The data suggest that mild perinatal hypoxia, causing transiently low Apgar scores, maybe sufficient to cause neuronal damage and affect cognition. Prolonged partial hypoxia tends to target the hemispheric grey matter and subcortical white matter. Despite considerable integration of different brain areas, logical thinking is associated with the ventrolateral prefrontal cortex and pre-supplementary motor cortex.

**Table 1 Clinical risk factors and social economic characteristics of the study population (n = 176 524)**

| Risk factor/characteristics                          | Data                                              |
|-----------------------------------------------------|---------------------------------------------------|
| **Antenatal/developmental factors**                 |                                                   |
| Parity                                              | 2 (1–2)                                           |
| Pre-eclampsia, No (%)                               | 15 394 (8.7)                                      |
| Birth weight (g)                                    | 3606 (491)                                        |
| Birth length (cm)                                   | 51.1 (2.1)                                        |
| Head circumference (cm)                             | 34.9 (1.5)                                        |
| **Intrapartum/neonatal factors**                    |                                                   |
| Maternal infection, No (%)                          | 2111 (1.2)                                        |
| Neonatal infection, No (%)                          | 314 (0.2)                                         |
| Mode of delivery, No (%)                            |                                                   |
| Vaginal                                             | 151 971 (88.1)                                    |
| Instrumental                                        | 13 306 (7.5)                                      |
| Caesarean section                                   | 11 247 (6.4)                                      |
| **Season of birth, No (%)**                         |                                                   |
| Spring                                              | 50 717 (28.7)                                      |
| Summer                                              | 43 984 (24.9)                                      |
| Autumn                                              | 40 636 (23.0)                                      |
| Winter                                              | 41 187 (23.3)                                      |
| Year of birth, No (%)                               |                                                   |
| 1973                                                | 44 779 (25.4)                                      |
| 1974                                                | 46 714 (26.5)                                      |
| 1975                                                | 43 593 (24.7)                                      |
| 1976                                                | 41 438 (23.5)                                      |
| **Maternal data**                                   |                                                   |
| Maternal age (years)                                | 26.5 (23.3–29.8)                                  |
| Maternal occupation, No (%)                         |                                                   |
| Manual worker                                       | 66 428 (37.6)                                     |
| Non-manual worker                                   | 80 213 (45.4)                                     |
| Self-employed                                       | 8170 (4.6)                                        |
| Other                                               | 21 713 (12.3)                                     |
| Maternal education status, No (%)                   |                                                   |
| <9 Years                                            | 28 935 (16.4)                                     |
| 9–10 Years                                          | 35 379 (20.0)                                     |
| Full secondary                                      | 68 253 (38.7)                                     |
| Higher education                                    | 43 957 (24.9)                                     |
| **Paternal data**                                   |                                                   |
| Paternal age (years)                                | 28.8 (25.8–32.2)                                  |
| Paternal occupation, No (%)                         |                                                   |
| Manual worker                                       | 63 453 (36.0)                                     |
| Non-manual worker                                   | 76 669 (43.4)                                     |
| Self-employed                                       | 17 657 (10.0)                                     |
| Other                                               | 18 745 (10.6)                                     |
| Paternal education status, No (%)                   |                                                   |
| <9 Years                                            | 49 120 (27.8)                                     |
| 9–10 Years                                          | 25 827 (14.6)                                     |
| Full secondary                                      | 61 758 (35.0)                                     |
| Higher education                                    | 39 819 (22.6)                                     |

Data are mean (SD), median (IQR) or number (%) as appropriate.
| Time to reach an Apgar score of >6 (min) | Measures of cognition          | Mean reduction (z-score) | p*                  | Measure of education | Mean reduction (z-score) | p*                  |
|----------------------------------------|-------------------------------|--------------------------|---------------------|----------------------|--------------------------|---------------------|
|                                        | Logic score (n = 134 996)     |                          |                     |                      |                          |                     |
|                                        | Synonym score (n = 133 858)   |                          |                     |                      |                          |                     |
|                                        | Spatial score (n = 133 825)   |                          |                     |                      |                          |                     |
|                                        | Technical score (n = 124 149) |                          |                     |                      |                          |                     |
|                                        | IQ score (n = 136 788)        |                          |                     |                      |                          |                     |
|                                        | School grade (n = 167 117)    |                          |                     |                      |                          |                     |
| <1                                     | Ref                           | Ref                      |                     | Ref                  | Ref                      |                     |
| 1–5                                    | 0.017 (−0.014−0.048)          | 0.006                    |                     | 0.018 (−0.048−0.015)  | 0.040                    |                     |
| >5                                     | 0.107 (0.036−0.179)           |                          |                     | 0.108 (0.035−0.181)  | 0.094 (0.022−0.167)      |                     |

Adjusted for antenatal factors

| <1                                     | Ref                           | Ref                      |                     | Ref                  | Ref                      |                     |
| 1–5                                    | 0.036 (0.005−0.067)           | −0.001                   |                     | 0.001 (−0.032−0.031)  | 0.040                    |                     |
| >5                                     | 0.120 (0.049−0.191)           |                          |                     | 0.119 (0.047−0.192)  | 0.100 (0.028−0.173)      |                     |

Adjusted for antenatal and intrapartum/neonatal factors

| <1                                     | Ref                           | Ref                      |                     | Ref                  | Ref                      |                     |
| 1–5                                    | 0.039 (0.008−0.070)           | −0.001                   |                     | 0.001 (−0.034−0.029)  | 0.057                    |                     |
| >5                                     | 0.123 (0.052−0.194)           |                          |                     | 0.116 (0.043−0.169)  | 0.096 (0.024−0.169)      |                     |

Adjusted for antenatal, intrapartum/neonatal and social factors

| <1                                     | Ref                           | Ref                      |                     | Ref                  | Ref                      |                     |
| 1–5                                    | 0.034 (0.005−0.063)           | 0.001                    |                     | 0.001 (−0.037−0.024)  | 0.088                    |                     |
| >5                                     | 0.092 (0.025−0.158)           |                          |                     | 0.081 (0.021−0.161)  | 0.071 (0.010−0.140)      |                     |

*p for trend.

†Parity, pre-eclampsia, birth weight, length and head circumference.

‡Mode of delivery, maternal or infant infection, season and year of birth.

§Maternal and paternal education status, occupation and age.
Table 3  Logistic regression models for the association of duration to achieve a normal Apgar score and poor score at cognitive testing

| Time to reach an Apgar score of >6 (min) | Measures of cognition | OR (95% CI) | p* | OR (95% CI) | p* | OR (95% CI) | p* | OR (95% CI) | p* | OR (95% CI) | p* | OR (95% CI) | p* |
|-----------------------------------------|-----------------------|-------------|----|-------------|----|-------------|----|-------------|----|-------------|----|-------------|----|
|                                         | Low logic score       |             |    |             |    |             |    |             |    |             |    |             |    |
|                                         | (n = 134 596)         | Unadjusted  | 1.00| 1.00         |    | 1.00         |    | 1.00         |    | 1.00         |    | 1.00         |    |
|                                         |                       | 1–5         | 1.20 (1.05 to 1.38)| 0.001| 1.04 (0.91 to 1.19)| 0.11| 1.01 (0.89 to 1.15)| 0.05| 1.19 (1.04 to 1.36)| 0.02| 1.09 (0.98 to 1.21)| 0.008|
|                                         |                       | >5          | 1.43 (1.05 to 1.94)|              | 1.30 (0.98 to 1.74)|              | 1.47 (1.12 to 1.93)|              | 1.13 (0.83 to 1.54)|              | 1.30 (1.04 to 1.64)|              |
|                                         |                       | Adjusted for antenatal factors | 1.00| 1.00         |    | 1.00         |    | 1.00         |    | 1.00         |    | 1.00         |    |
|                                         |                       | 1–5         | 1.26 (1.10 to 1.44)| <0.001| 1.10 (0.96 to 1.25)| 0.03| 1.03 (0.91 to 1.18)| 0.03| 1.19 (1.04 to 1.37)| 0.02| 1.12 (1.01 to 1.25)| 0.002|
|                                         |                       | >5          | 1.43 (1.06 to 1.94)|              | 1.33 (1.00 to 1.79)|              | 1.45 (1.11 to 1.91)|              | 1.09 (0.80 to 1.49)|              | 1.31 (1.04 to 1.65)|              |
|                                         |                       | Adjusted for antenatal and intrapartum/neonatal factors | 1.00| 1.00         |    | 1.00         |    | 1.00         |    | 1.00         |    | 1.00         |    |
|                                         |                       | 1–5         | 1.26 (1.10 to 1.44)| <0.001| 1.11 (0.97 to 1.27)| 0.01| 1.03 (0.90 to 1.17)| 0.03| 1.20 (1.05 to 1.38)| 0.02| 1.14 (1.03 to 1.27)| 0.001|
|                                         |                       | >5          | 1.43 (1.06 to 1.94)|              | 1.36 (1.02 to 1.82)|              | 1.46 (1.11 to 1.91)|              | 1.09 (0.80 to 1.49)|              | 1.35 (1.07 to 1.69)|              |
|                                         |                       | Adjusted for antenatal, intrapartum/neonatal factors and social factors | 1.00| 1.00         |    | 1.00         |    | 1.00         |    | 1.00         |    | 1.00         |    |
|                                         |                       | 1–5         | 1.25 (1.10 to 1.43)| <0.001| 1.09 (0.96 to 1.25)| 0.04| 1.02 (0.90 to 1.16)| 0.08| 1.18 (1.04 to 1.35)| 0.04| 1.14 (1.03 to 1.27)| 0.003|
|                                         |                       | >5          | 1.34 (1.01 to 1.78)|              | 1.26 (0.95 to 1.67)|              | 1.37 (1.05 to 1.77)|              | 1.03 (0.77 to 1.39)|              | 1.35 (1.07 to 1.69)|              |

*p for trend.
†Parity, pre-eclampsia, birth weight, length and head circumference.
‡Mode of delivery, maternal or infant infection, season and year of birth.
§Maternal and paternal education status, occupation and age.
Synonym identification is associated with the dominant parietal association cortex, and spatial tasks with the non-dominant parietal association cortex. Thus the spectrum of cognitive changes in this study is compatible with mild prolonged partial hypoxic injury to the brain at term. Another possibility is that prenatal disease, including the effects of gene polymorphisms, uncontrolled for in these analyses, may present with poor Apgar scores and predispose to later cognitive dysfunction. We have attempted to control for likely important confounders in our analyses, but some degree of residual confounding is possible. The prevalences seen in our data are consistent with the published literature—for example, the population risk for neonatal septicemia/meningitis (2.3/1000) is similar to that found in comparable studies (2.8/1000). Another explanation may be that infants who received resuscitation developed cognitive defects owing to their exposure to high concentrations of oxygen, and not the underlying cause of their poor birth condition.

Comparisons with other studies

We are not aware of any previous studies that have found an association between a transiently low Apgar score and cognitive defects in subsequently well infants. Sedman et al were unable to show an association between low Apgar scores and IQ at 18 years. Most et al and Blackman reported evidence of reduced cognition only in infants who had developed signs of encephalopathy after birth. It is likely that there was limited power in these studies to detect the modest association seen here. However, the modest effect means that the absolute risk increase of a low IQ score for an individual infant with a briefly low Apgar score is only 0.7%, and 2.4% for infants with prolonged low Apgar scores. The score used in this study has previously been approximated to the more conventional IQ scale (with mean score 100), and on this scale, the proportion of men in this study with a low IQ score (below 81) estimated to be due to all transiently low Apgar scores is only 94 (0.7%) out of a total of 13 448, while infants with briefly low Apgar scores only showed a reduction in mean IQ of 0.5 points, and those with prolonged low Apgar scores a reduction of 1.2 points.

CONCLUSIONS

Infants in poor condition at birth have an increased risk of poor functioning in cognitive tests at age 18, even if the infants recovered quickly and did not develop encephalopathy. This association is modest and unlikely to be of clinical significance for individual infants.

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