Birthweight ratio and outcome in preterm infants

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Abstract

The association between birthweight ratio and outcome was investigated in 429 infants born before 31 weeks' gestation. Birthweight ratio was calculated in each case as birth weight divided by mean birth weight for gestation (from reference data). It was shown that a given ratio corresponded to the same birth centile across the gestational age range studied; a ratio of 0.8 corresponding to the 10th centile. There was a linear relationship between birthweight ratio and requirement for mechanical ventilation and postneonatal mortality. Birthweight ratio was also strongly and linearly related to body weight, length, and head circumference at 18 months' corrected age. Overall, there was no association between this ratio and neurodevelopmental outcome to 18 months. However, the subgroup with the largest weights for gestation (birthweight ratio ≥ 1.1), had significantly higher language subscores than all the other children.

Our data show that conventional dichotomous categorisation of preterm infants into small or appropriate for gestation is inadequate when exploring the association between size for gestation and outcome.

Babies born small for gestation have been regarded as a special and high risk group. It has been suggested that such infants may have an increased rate of mortality or later neurodevelopmental impairment and reduced longer term growth potential.¹⁻⁵ It is well recognised that very preterm infants also constitute a high risk group for an impaired outcome. There is conflicting information, however, on the outlook for preterm infants in relation to their size for gestation at birth.⁶⁻¹¹ Most studies have been small and many have either matched for birth weight or compared small and appropriate for gestational age infants within a cohort which is defined by an upper birthweight criterion, thus excluding the larger infants at some gestational ages. Furthermore, the customary approach of comparing outcomes in 'small for gestation' with 'appropriate for gestation' infants, when the latter group comprises all from the 10th through the 99th centile, has never been satisfactorily justified.

Brooke *et al*, in a study of factors influencing birth weight, derived a continuous variable to define size for gestation, termed the 'birthweight ratio'.¹² This ratio was calculated as the infant's birth weight divided by reference median birth weight for the baby's gestation.

Thus a birthweight ratio of 1 would signify that a baby's weight was on the 50th centile, whereas with a ratio of 0.80 a baby would be 20% lighter than the median. For birthweight ratio to be used for prognostic purposes in preterm infants of widely varying gestations, however, it would be important that a given value of this ratio corresponded to the same birth centile at different gestations. Having confirmed that this was the case (see below), birthweight ratio was calculated for 429 infants of less than 31 weeks' gestation, and data were examined for associations between birthweight ratio and outcome in the neonatal period and at 18 months' post term.

Subjects and methods

The 429 infants in this study were from a larger five centre trial on feeding in babies weighing less than 1850 g at birth.¹³ We report here on all enrolled infants born before 31 weeks of gestation, as above that gestation the larger infants (>1850 g) would have been excluded. Examination of records in all the centres confirmed that no infants of 30 weeks' gestation or less had a birth weight over 1850 g. Infants were enrolled in the trial within the first 48 hours of life; 53 eligible infants (without major congenital malformation and with median gestational age 26 weeks) died before enrolment.

Extensive social data were collected for each baby at parental interview. Social class was coded using the Registrar General's Classification,¹⁴ with social class 3 subdivided into manual and non-manual. Maternal education was categorised as: 1, no educational qualifications; 2, less than four passes in the certificate of secondary education examination (CSE); 3, four or more CSE's or any 'O' level passes; 4, any 'A' level passes; and 5, degree or higher professional qualification. Birth rank was the birth order of the child in the living children of the family, with those from multiple births assigned equal rank. Details of neonatal course were recorded prospectively.

Birthweight ratio was calculated as the ratio of each infant's birth weight to a reference value of median birth weight for the baby's gestation. This reference value was taken from data, previously published,^{15 16} for babies from the same cohort born after spontaneous onset of labour in the five centres. Infants born by elective caesarean section had been excluded from these reference statistics because their inclusion would have resulted in a group heavily biased by growth retarded infants who are often delivered interventively. The reference data were also used to calculate the correspondence

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Accepted 28 August 1989

between birth centile and birthweight ratio, and, as an important aspect of validation, to show the constancy of this correspondence across gestational age groups.

Surviving infants were invited for follow up examination at 18 months from expected date of delivery. Children from the four East Anglian centres (Cambridge, Ipswich, King's Lynn, and Norwich) were examined by RM; RP organised follow up in the fifth centre, Sheffield. An extensive history was taken for each child, followed by physical and neurological examination, using the method described by Amiel-Tison and Grenier.¹⁷ Naked weight, length (to the next succeeding mm using a horizontal stadiometer), and occipitofrontal head circumference (to the next succeeding mm using paper tape) were measured in each case. Several developmental tests were administered; Bayley mental and motor scales,¹⁸ Vineland social maturity scale,¹⁹ and the questionnaire based academic scale of developmental profile II.²⁰ Scores for each child were calculated using the child's age from expected date of delivery (that is, corrected for prematurity). Mental and psychomotor development indices were derived from the results on the Bayley scales, social quotient from the Vineland test, and IQ equivalent was calculated using the academic scale of developmental profile II.

Student's *t* and χ^2 were used for univariate analyses. Regression analysis was used where adjustment for confounding factors was required (linear for continuous and logistic for dichotomous dependent variables).

Results

In order to explore whether the correspondence of birth centile and birthweight ratio was similar across gestational age groups, the ratio corresponding to 3rd, 10th, 90th, and 97th centiles was calculated for each gestation from the smoothed reference data referred to above.¹⁵

Figure 1 Distribution of birthweight ratios within the study cohort.

(For example, the ratio corresponding to the 10th centile at 28 weeks = weight on the 10th centile at 28 weeks divided by median weight at 28 weeks.) The ratio was remarkably constant, at gestations from 25 to 30 weeks, for any of the four centiles studied. Thus for the 3rd centile, the ratio only varied between 0.70 and 0.72 across gestational age groups. Corresponding values for the 10th centile were 0.80–0.81; the 90th centile: 1.19–1.20, and the 97th centile 1.28–1.30. The figures are consistent with a birthweight ratio that is normally distributed with a constant coefficient of variation across gestations of 15%.

The distribution of birthweight ratio within the 429 infants in this cohort is shown in fig 1. The distribution (range 0.39 to 1.51) shows the expected left shift, reflecting the increased proportion of small for gestation infants, largely delivered interventively, found among those born preterm.¹⁵

The association between an infant's birthweight ratio and those social and demographic factors known to have an important influence on later developmental status²¹ was investigated. Birthweight ratio was not significantly related to social class, birth rank, or sex of the child or to maternal age, education, or marital status.

Length of gestation was investigated for association with birthweight ratio. Infants were divided into the five birthweight ratio categories: <0.8, 0.8–0.9, 0.9–1, 1–1.1, and ≥ 1.1 , giving groups of broadly comparable size. Infants in the lowest ratio group (<0.8) were all less than the 10th centile and would be classified in many studies as small for gestation. There were no significant differences in mean gestation between the five birthweight ratio categories (table 1), though there were variations (range 28.1–28.8 weeks). In subsequent analyses outcome data are presented by birthweight ratio category (as above). In addition, regression analysis has been used to relate birthweight ratio, as a continuous variable, to each outcome, while adjusting for gestation, to ensure that the small differences in gestation between birthweight ratio categories did not confound the analysis.

No association was found between birthweight ratio category and mortality in the first 28 days (table 1). Infants were enrolled in this study within the first 48 hours, however, so those dying soon after birth would have been excluded. There was evidence, however, of higher postneonatal mortality with decreasing birthweight ratio group. This association was highly significant when logistic regression analysis was used to relate ratio (as a continuous variable) to postneonatal mortality, adjusting for gestational age ($p < 0.001$).

Birthweight ratio was related to the duration of mechanical ventilation. For this analysis data from the 45 babies who died in the first 28 days were excluded, as early death would have curtailed the period of respiratory illness. There were 384 survivors of the neonatal period, of whom 200 were boys. Table 2 shows the proportion of infants in each ratio group requiring mechanical ventilation in the first 24 hours, for

Table 1 Birthweight ratio and mortality

	Birthweight ratio groups				
	<0.8 (n=71)	0.8 to <0.9 (n=74)	0.9 to <1.0 (n=104)	1.0 to <1.1 (n=94)	≥1.1 (n=86)
Mean (SE) gestation (weeks)	28.8 (0.15)	28.3 (0.17)	28.1 (0.15)	28.1 (0.14)	28.5 (0.15)
No (% occurrence) dying in first 28 days*	4 (6)	8 (11)	15 (14)	9 (10)	9 (10)
No (% occurrence) dying postneonally	8 (11)	9 (12)	6 (6)	3 (3)	0 (0)***

*Infants were enrolled in this study within 48 hours of birth, therefore very early neonatal deaths are not included.

***p<0.001 for birthweight ratio (as a continuous variable) regressed against whether each subject died in the postneonatal period (adjusting for gestation).

Table 2 Birthweight ratio and requirement for mechanical ventilation (infants dying in the neonatal period are excluded from these analyses)

	Birthweight ratio groups				
	<0.8 (n=67)	0.8 to <0.9 (n=66)	0.9 to <1.0 (n=89)	1.0 to <1.1 (n=85)	≥1.1 (n=77)
No (%) ventilated in first 24 hours	54 (81)	57 (86)	71 (80)	64 (75)	48 (62)***
No (%) ventilated >7 days	26 (39)	23 (35)	26 (29)	25 (29)	17 (22)***
No (%) ventilated >14 days	15 (22)	15 (23)	16 (18)	14 (16)	4 (5)***
No (%) ventilated >28 days	7 (10)	7 (11)	9 (10)	7 (8)	1 (1)**

p<0.005, *p<0.0005, for birthweight ratio (as a continuous variable) regressed against the need for ventilation in the first 24 hours and for over 7, 14, or 28 days (adjusting for gestation).

more than seven days, more than 14 days, and more than 28 days. There was a significant association between ratio group and need for mechanical ventilation at each of these cutoff values (respectively: p<0.025, p<0.001, p<0.025, and p<0.001, using χ^2 test for trend). These associations were confirmed using logistic regression analysis, adjusting for gestational age (respectively: p<0.0005, p<0.0005, p<0.0005, and p<0.005).

Altogether 329/358 (92%) of surviving infants were examined at 18 months post term. Mean weight, length, and head circumference at 18 months is shown for each ratio group in table 3. There was a progressive increase in each of these growth measures with increasing birthweight ratio (p values for trend were respectively <0.0001, <0.0001, and <0.002). While data are shown for both sexes combined, very similar trends were seen when data from boys and girls were analysed separately (as expected, there was a consistent trend to higher values for body weight, length, and head circumference in boys). Although there were no significant differences in sex distribution between ratio groups, there were variations that could have confounded the analyses above. Regression models were therefore used to explore the association between anthropometry at 18 months (dependent variable) and birthweight ratio (as a continuous variable), after adjusting for the sex

of the child as well as gestation. There were highly significant associations between birthweight ratio and weight and length (both p<0.0001) and head circumference (p<0.003) at 18 months' post term.

It is of interest that of the 329 children seen at follow up, 143 (43%) had birthweight ratios of 1.0 or more, indicating that their weight at birth was on or above the 50th centile, whereas at 18 months, only 75 (23%) had weights on or above the 50th centile, using the Whitehead standards (unpublished data).²²

The number of children in each ratio group diagnosed as having neurological impairment (including those with little or no handicap) is shown in table 4. There were no significant differences between the groups. If these impaired children are combined with those whose Bayley mental development index was less than 70, to form a group we have described here as 'neurodevelopmentally impaired' there was again no significant difference between birthweight ratio groups. There was no significant association between ratio group and either mean Bayley mental score, Bayley motor score (table 4), IQ equivalent or social quotient, whether or not children with neurological impairment were included in the analysis. Regression analysis, adjusting for gestational age, sex and birth rank of the child, social class, and maternal age and education also failed to show any association

Table 3 Birthweight ratio and growth to 18 months post term*

	Birthweight ratio groups				
	<0.8	0.8 to <0.9	0.9 to <1.0	1.0 to <1.1	≥1.1
No followed up	56	54	76	77	66
Mean (SD) body weight (kg)	9.3 (1.2)	9.9 (1.3)	10.2 (1.1)	10.2 (1.2)	10.7 (1.3)***
Mean (SD) body length (cm)	77.7 (3.5)	79.0 (3.3)	79.7 (3.3)	80.1 (3.2)	80.7 (3.0)***
Mean (SD) head circumference (cm)	47.4 (1.6)	47.9 (1.9)	48.2 (1.7)	48.2 (1.5)	48.3 (1.5)**

*For reference the 50th centile (sexes combined) for weight, length, and head circumference at 18 months is: 10.7 kg, 80.3 cm, 48.7 cm; and the 10th centile: 9.5 kg, 76.8 cm, 46.8 cm.

p<0.003, *p<0.0001, for birthweight ratio (as a continuous variable) regressed against either weight, length, or head circumference, adjusting for sex and gestation.

Table 4 Birthweight ratio and neurodevelopmental outcome at 18 months

	Birthweight ratio groups				
	<0.8	0.8 to <0.9	0.9 to <1.0	1.0 to <1.1	≥1.1
No followed up	56	54	76	77	66
No (%) with neurological impairment	5 (9)	4 (7)	12 (16)	8 (10)	9 (14)
No (%) with neurodevelopmental impairment*	5 (9)	8 (15)	16 (21)	14 (18)	12 (18)
Mean (SD) Bayley mental development index	100 (17)	98 (20)	99 (17)	99 (21)	103 (20)
Mean (SD) Bayley motor development index	91 (19)	88 (16)	90 (19)	86 (20)	88 (17)
Mean (SD) language subscore as quotient	96 (18)	93 (18)	92 (20)	96 (19)	101 (19)**

*Neurodevelopmental impairment was diagnosed as neurological impairment or mental index <70.

**p<0.01, for language subscore in infants with birthweight ratios 1.1 or above compared with all infants with a ratio <1.1.

between birthweight ratio and these measures of developmental outcome.

When the language score was calculated (using the Kent scoring adaptation of the Bayley mental scale²³), however, those in the highest ratio group (ratio 1.1 or above) had a significantly higher mean score than the other groups combined (p<0.01). Conversely, those in the lowest ratio group (infants who would usually be categorised as small for gestation) did not differ from the other groups combined. Regression analyses (adjusted as above) confirmed that those children in the highest ratio group (≥1.1) had significantly higher language scores than either those in all other groups combined (p<0.005) or in a 'control group' of babies with ratios of 0.9 to 1.1, in the middle of the normal range (p<0.05). Conversely, similar regression analyses confirmed that there was no difference in language score for children in the lowest ratio group compared with those in the other groups combined (ratio 0.8 and above), or those with ratios 0.9–1.1.

Discussion

Our study has shown that weight for gestation is a major factor relating to short term morbidity and postneonatal mortality and to longer term growth and language development. Nevertheless, as we argue below, the data presented show that in outcome studies of preterm infants, the conventional approach of dividing infants arbitrarily into 'small' (<10th centile) and 'appropriate' (≥10th centile) for gestation may be quite inadequate to describe the influence of birth weight relative to gestation.

Distribution of birthweight ratios within this group of 429 infants born before 31 weeks of gestation differed from that expected in an unselected population. Many infants in this group were delivered interventively because of intrauterine growth retardation or maternal hypertension, reflecting the substantially increased proportion of small for gestational age infants seen among those undergoing modern neonatal intensive care.¹⁵

We observed that with increasing birthweight ratio there was a progressive and significant decrease in the need for mechanical ventilation, when the latter was expressed either as a continuous variable (days of ventilation) or as a series of dichotomous variables (proportion of subjects requiring ventilation in the first 24 hours and beyond either 7, 14, or 28 days). Our findings indicate therefore that the incidence of chronic lung disease diminishes with increasing body size for gestational age. As an example

fig 2 shows the estimated proportion of subjects born at 27 weeks' gestation requiring ventilation in each of the five, approximately equally sized birthweight ratio categories. Estimates are based on absolute odds calculated from logistic regression analyses. Data shown in this figure emphasise that the association between size for gestation and requirement for mechanical ventilation is linear across the entire range of birthweight ratio categories. Thus to compare infants in the lowest ratio category (<0.8, <10th centile) with the remainder would be arbitrary and would not result in adequate biological description of the data.

Our data on requirement for mechanical ventilation in surviving infants would lead us to expect that neonatal mortality might be higher with decreasing ratio. We were, however, unable to show the expected increase in mortality in the first 28 days with lower birthweight ratio, though we might have missed such a relationship as a result of recruiting most infants between 24 and 48 hours after birth, before which there might have been a selective loss of infants in the lowest birthweight ratio categories. Nevertheless, for postneonatal mortality (after 28 days), there was indeed a pronounced linear decline with increasing birthweight ratio. It is clear from the mortality data in table 1 that it would have been inappropriate to have categorised infants into 'small' and 'appropriate' for gestational age.

Figure 2 The estimated proportion of 27 week infants in each birthweight category requiring mechanical ventilation in the first 24 hours and beyond 7, 14, and 28 days. (Calculated from absolute odds based on logistic regression analysis.)

In many studies on small for gestational age infants born at term, long term growth potential has been shown to be impaired.^{4 5} Corresponding data for growth retarded infants born preterm are more limited.^{24 25} In this study birthweight ratio was a powerful predictor of weight, length, and head circumference, even after adjustment for the potentially confounding factors. The association between growth and birthweight ratio was again linear across all birthweight ratio categories, the infants with the highest ratios exhibiting the largest birth weight, length, and head circumference values. As a whole the infants investigated here were growth retarded at 18 months. The proportion of infants above the 50th centile for birth weight was 43%; whereas only 23% of infants were over the 50th centile for weight at 18 months.²² Indeed at 18 months even the infants from the highest birthweight ratio category (ratio ≥ 1.1), had mean body weight and length close to the 50th centile and mean head circumference below the 50th centile (sexes combined). Thus the larger the birthweight ratio, the greater the chance that the infant had attained average body size at 18 months. A dichotomous categorisation of infants into those above or below the 10th centile, would not have been adequate to demonstrate these findings.

Some studies have indicated that preterm small for gestational age infants have reduced developmental performance in childhood.^{6 10 11} We were unable to confirm this using a battery of developmental tests, including Bayley mental and psychomotor scales, the Vineland social maturity and the academic scale of developmental profile II. Interestingly, only the language score (from the Kent subscores of the Bayley mental scale) showed an association with size for gestation and in this instance it was only the infants with the largest birthweight ratios (≥ 1.1) that were advantaged compared with the others. Planned follow up examinations in later childhood will investigate whether birthweight ratio is associated with differences in later IQ or learning performance.

Usher and McLean (RH Usher, FH McLean, unpublished data) have suggested that infants who are large for gestational age and born at term are disadvantaged in terms of developmental outcome; this, however, might relate to the strong positive association between maternal diabetes and birth weight. In contrast, in this study on very preterm infants, it was the infants with the largest body size for gestation who were significantly advantaged in short and long term outcome. Nevertheless, the association between birth weight and outcome in more mature preterm and term infants needs to be re-explored using birthweight ratio as a prognostic index. Results would be broadly similar if birthweight centile groups (<10th, 10th–25th, etc) were used, though for the researcher a continuous variable like birthweight ratio has advantages over a categorical one like centile

strata. Furthermore, birthweight ratio is a more direct measure of birth weight for gestation.

In conclusion, our findings show that with increasing birth weight for gestation, preterm infants had a progressively better prognosis in terms of their need for respiratory support, or death in the early months, and had a progressively improved long term growth performance. Our observations suggest that an arbitrary dichotomous categorisation into small or appropriate for gestation groups is inadequate as a prognostic index in preterm infants.

We gratefully acknowledge the help and cooperation of the paediatricians in Cambridge, Ipswich, Kings Lynn, Norwich, and Sheffield, and Farley Health Products Limited for financial help.

- 1 Usher RH, McLean FH. Normal fetal growth and the significance of fetal growth retardation. In: Davis JA, Dobbing J, eds. *Scientific foundations of paediatrics*. 1st ed. London: Heinemann, 1974:69–80.
- 2 Ellenberg JH, Nelson KB. Birthweight and gestational age in children with cerebral palsy or seizure disorders. *Am J Dis Child* 1979;133:1044–8.
- 3 Neligan GA, Kolvin I, Scott DM, et al. Born too soon or born too small. A follow up study to seven years of age. *Clinics in development medicine*. Philadelphia: Lippincott, 1976:61.
- 4 Fitzhardinge PM, Steven EM. The small for dates infants. i. later growth patterns. *Pediatrics* 1972;49:671–81.
- 5 Davies DP. Growth of 'small-for-dates' babies. *Early Hum Dev* 1981;5:95.
- 6 Pena IC, Teberg AJ, Finells KM. The premature small-for-gestational-age infant during the first year of life: comparison by birthweight and gestational age. *J Pediatr* 1988;113:1066–73.
- 7 Eaves LC, Nuttall JC, Klonoff H, et al. Development and psychological test scores in children of low birthweight. *Pediatrics* 1970;45:9–20.
- 8 Vohr BR, Oh W, Rosenfield AG, et al. The preterm small-for-gestational age infant: A two-year follow-up study. *Am J Obstet Gynecol* 1979;133:425–31.
- 9 Vohr BR, Hack M. Developmental follow-up of low birthweight infants. *Pediatr Clin North Am* 1982;29:1441–54.
- 10 Fitzhardinge PM, Kalman E, Ashby S, et al. Present status of the infant of very low birthweight treated in a referral neonatal intensive care unit in 1974. In: Ciba Foundation Symposium 59. *Major mental handicap: methods and costs of prevention*. New York: Excerpta Medica, 1978:139–50.
- 11 Francis-Williams J, Davies PA. Very low birthweight and later intelligence. *Dev Med Child Neurol* 1972;14:563–74.
- 12 Brooke OG, Anderson HR, Bland JM, et al. Birthweight, stress and behaviour; principal results from a prospective population study. *Br Med J* 1989;298:795–801.
- 13 Lucas A, Gore SM, Cole TJ, et al. A multicentre trial on the feeding of low birthweight infants: effects of diet on early growth. *Arch Dis Child* 1984;59:722–30.
- 14 Registrar General. *Classification of occupations*. London: HMSO, 1980.
- 15 Lucas A, Cole TJ, Gandy GM. Birthweight centiles in preterm infants reappraised. *Early Hum Dev* 1986;13:313–22.
- 16 MRC Dunn Nutrition Unit. *Reference chart; birthweight centiles for preterm infants under 32 weeks' gestation*. Ware: Castlemead Publications, 1986.
- 17 Amiel-Tison C, Grenier A. *Neurological assessment during the first year of life*. Oxford: Oxford University Press, 1986.
- 18 Bayley N. *Bayley scales of infant development*. New York: Psychological Corporation, 1969.
- 19 Doll EA. *Vineland social maturity scale*. Circle Pines, Minnesota: American Guidance Service, 1965.
- 20 Alpern GD, Boll TJ, Shearer MS. *Development profile II*. Aspen, Colorado: Psychological Development Publications, 1980.
- 21 Morley R, Cole TJ, Powell R, Lucas A. Mother's choice to provide breast milk and development outcome. *Arch Dis Child* 1988;63:1382–5.
- 22 Whitehead RG, Paul AA, Cole TJ. Diet and growth of healthy infants. *Journal of Human Nutrition and Dietetics* 1989;2:73–84.
- 23 Reuter J, Stancin T, Craig P. *The Kent scoring adaptation of the Bayley scales of infant development*. Kent, Ohio: Kent Developmental Metrics, 1981.
- 24 Hack M, Merikatz IR, McGrath SK, et al. Catch-up growth in very low birthweight babies: potential and clinical correlates. *Am J Dis Child* 1984;138:370–5.
- 25 Tudhope DS, Burns Y, O'Callaghan M, et al. The relationship between intrauterine and postnatal growth on subsequent psychomotor development in very low birthweight infants. *Aust Paediatr J* 1983;19:3–8.