ORIGINAL ARTICLE

Fetal growth restriction: relation to growth and obesity at the age of 9 years

Supratik Chakraborty, Desaline Veronica Joseph, Michael John Gordon Bankart, Stewart A Petersen, Michael P Wailoo

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See end of article for authors' affiliations

Correspondence to: Dr Michael P Wailoo, Senior Lecturer in Child Health, Robert Kilpatrick Clinical Sciences Building, University of Leicester, PO Box: 65, Leicester LE2 7LX, UK; mw33@leicester.ac.uk

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Objective: To assess growth patterns of 9-year-old children, some of whom had intrauterine growth restriction (IUGR).
Method: 75 9-year-old children (41 were IUGR infants) were weighed and measured at birth, at 1 year, at 2 years and at 9 years of age. Using general linear models for continuous data, changes in weight z scores were used to quantify growth rate between birth and 9 years of age.
Results: IUGR children were smaller at birth (weight z score −2.1 *v* 0.2 in normal children; $p<0.001$) but showed a greater increase in their weight between birth and 9 years (change of weight z score 1.5 *v* 0.4 in normal children; $p = 0.001$). At the age of 9 years the weight, height and body mass index (BMI) z scores were lower in IUGR children than the control children (weight z score −0.4 *v* 0.6, respectively; $p<0.001$, height z score −0.5 *v* 0, respectively; $p = 0.002$, BMI z score −0.2 *v* 0.7, respectively; $p = 0.002$). The predictors of these differences were IUGR, birth weight and maternal and paternal heights.
Conclusion: IUGR infants grow faster but remain shorter and lighter than their normal counterparts—that is, they fail to fully catch up by 9 years of age.

Intrauterine malnutrition leads to reduction in body size and weight at birth and is thought to have continuing influence on growth patterns into childhood.[1] However, there are conflicting views about whether growth-restricted babies ever completely recover potential lost body mass and catch up in size with the normal population. Some feeding methods used in growth-restricted newborns have been designed to produce catch-up weight gain, but instead may have led to obesity in some children,[1] a view, however, not universally supported.[2–4] This has been the basis for the theory that premature cardiovascular and metabolic diseases in adults may be promoted by a combination of growth restriction in utero and later catch-up growth and obesity.[5] This, if true, would give added importance to the later growth patterns of children with intrauterine growth restriction (IUGR) and provide an opportunity for the early identification and possible prevention of serious illness in adulthood.

We report on the pattern of growth seen in a group of children who were originally growth-restricted infants and who at the age of 9 years have been participating in a study of cardiovascular status.

METHODS

In an original study of postnatal developmental physiology we used serial antenatal ultrasound scanning to identify fetal growth restriction.[6] Any baby with a fetal abdominal girth two or more standard deviations below the mean or who by birth weight was below the second centile at term was deemed to be IUGR. During this initial study, all infants were weighed regularly and deep body temperature monitored at regular intervals, until there were no longer any changes in deep body temperature with sleep.

Now that those IUGR children are about 9 years old, they were recalled for a new study of their cardiovascular status. For comparison we chose controls from a large database of healthy children, who had shown normal fetal growth, were delivered at term and had normal birth weight, and who had been studied previously within the same developmental physiology project. The children in the control group were age matched with the IUGR children. All children had their height and weight measured; the height by a portable Harpenden stadiometer to the nearest millimetre and the weight by a Marsden Professional Physician Scale to the nearest 100 g. The heights of the mothers were also measured similarly. Paternal heights were mostly self-reported. As part of the normal health surveillance scheme for under-fives, weights and heights of the children were measured at intervals and recorded in the "Red Book" or parent held record.

For the purpose of the cardiovascular study each child had a full medical examination, and 24-h recording of ECG and ambulatory blood pressure. This is a report of the changes in body weight and height; cardiovascular changes will be reported elsewhere.

Collation of data

Information including medical conditions, medications taken, birth and perinatal data, heights of parents, and heights and weights of children at different ages was extracted onto a spreadsheet for analysis.

Analysis of weight and height data

We used the commercially available United Kingdom Growth Standards Data Analysis software (LMS Research Disc, Harlow Healthcare, Tyne and Wear, UK) to convert all the weight, height and body mass index (BMI) measurements into age and sex corrected corresponding standard deviation (z) scores with reference to 1990 British growth reference charts.

The z score is a statistical measure of the distance (measured in standard deviations) from the mean of a dataset in a gaussian population. A z score of 0 is at the mean of the population and a z score of +1 or −1 means that the value is 1 SD above or below the mean, respectively. z Score values between +2 and −2 cover 95% of the values in a gaussian

Abbreviations: BMI, body mass index; IUGR, intrauterine growth restriction

Table 1 Unadjusted continuous and categorical variables and their comparisons

Continuous variables	IUGR n = 41 Mean (95% CI)	Control n = 3 Mean (95% CI)	Difference of means (95% CI)	Probability value
Gestation (weeks)	38.98 (38.56 to 39.40)	39.18 (38.86 to 39.49)	−0.2 (−0.7 to 0.3)	0.45
Birth weight (kg)	2.56 (2.43 to 2.69)	3.53 (3.36 to 3.69)	−1.0 (−1.2 to −0.8)	<0.001
Birth weight z score	−2.1 (−2.3 to −1.8)	0.1 (−0.1 to 0.4)	−2.2 (−2.6 to −1.8)	<0.001
Placental weight (g)*	488 (448 to 528)	631 (583 to 679)	−143 (−203 to −82)	<0.001
Breast feeding duration (weeks)	4.2 (1.9 to 6.5)	10.5 (7.9 to 13)	−6.3 (−9.7 to −2.8)	0.001
Maternal height (cm)†	161.8 (159.2 to 164.4)	161.7 (158.9 to 164.4)	0.2 (−3.6 to 3.9)	0.93
Paternal height (cm)†	175.0 (172.5 to 177.6)	178.2 (176.3 to 180.1)	−3.2 (−6.3 to 0.03)	0.052
Current IMD score‡	21.2 (15.9 to 26.5)	12.9 (9.1 to 16.8)	8.3 (1.6 to 14.9)	0.02
Current age (years)	9.36 (9.12 to 9.54)	8.96 (8.78 to 9.23)	0.4 (0.09 to 0.7)	0.01
Final weight (kg)	28.32 (26.78 to 30.46)	32.64 (30.48 to 34.80)	−3.8 (−6.5 to −1.1)	0.007
Final weight z score	−0.4 (−0.7 to −0.1)	0.6 (0.3 to 1.0)	−1 (−1.5 to −0.5)	<0.001
Change in weight (kg)	26.26 (24.49 to 28.03)	29.53 (26.95 to 31.27)	−2.9 (−5.6 to −0.1)	0.04
Change in weight z score	1.7 (1.3 to 2)	0.5 (0.1 to 1)	1.2 (0.6 to 1.8)	<0.001
Final height (cm)	131.4 (129.3 to 133.4)	133.8 (132 to 135.5)	−2.4 (−5.1 to 0.3)	0.08
Final height z score	−0.6 (−0.9 to −0.3)	0.16 (−0.1 to 0.5)	−0.8 (−1.2 to −0.4)	0.001
Final BMI	16.63 (15.83 to 17.42)	18.11 (17.22 to 19)	−1.5 (−2.7 to −0.3)	0.01
Final BMI z score	−0.1 (−0.4 to 0.3)	0.8 (0.4 to 1.1)	−0.8 (−1.3 to −0.3)	0.002

Categorical variables	IUGR n = 41 Number (%)	Control n = 34 Number (%)	Probability value
Sex			0.12
Male	19 (46)	22 (64)	
Female	22 (54)	12 (36)	
Breast fed	19 (46)	25 (74)	0.02
Maternal smoking in pregnancy	16 (39)	9 (27)	0.25
Current smoking	21 (51)	12 (35)	0.17
Major medical problem	12 (29)	4 (12)	0.07
Currently on medication	11 (27)	4 (12)	0.16
Normal development	37 (90)	34 (100)	0.11
Mainstream schooling	40 (97)	34 (100)	0.36

Probability values were derived from t tests for continuous variables and from χ^2 tests for categorical variables.
*Placental weights were available for 35 children in the intrauterine growth restriction (IUGR) group and for 32 children in the control group.
†Maternal and paternal heights were available for 39 children in the IUGR group.
‡Index of multiple deprivation (IMD) score is a measurement of socioeconomic deprivation which is inversely related to deprivation.

population. By using z scores we have standardised our data by reference to the 1990 population mean. Changes of weight z scores were calculated between birth and final weight.

We carried out the statistical analysis using SAS version 9.1.3 for Windows. To determine whether the difference in z scores between the two groups was significant at the various ages of measurement, multivariable general linear models were applied to the data. These models are an extension of multiple linear regression models, in which there is a continuous dependent variable, and a combination of continuous and categorical independent variables, the aim being to quantify the relationship between the predictors and the dependent variable, and to find the best predictors. Potential candidate predictors were: IUGR; duration of breast feeding; whether breast fed or not; maternal height; estimated paternal height; mean parental height; current smoking status in household; maternal smoking status in pregnancy; Indices of Multiple Deprivations (IMD 2004); sex; presence of a major medical problem; and current use of medication.

IMD 2004 is a measure of multiple deprivation at the small area level defined as Lower Layer of Super Output Area (SOA), which was developed from the 2001 census to improve reporting of statistical data. The lower layer of SOA, on which IMD 2004 is based, typically represents an area with a minimum population of 1000 and mean population of 1500, and is more reflective of local population than a much larger electoral ward. The IMD 2004 contains seven domains of deprivation: income; employment; health and disability; education and training; barriers to housing; living environment; and crime.

Univariable analyses were used to narrow the selection process by eliminating variables with a probability >0.1 of predicting each dependent variable, and then the remaining variables were entered into a multivariable main effects model using a backward stepwise procedure. Significant interactions were then explored. We used this method owing to the small number of subjects per candidate predictor variable.

RESULTS

We identified 127 children from the original study (64 IUGR and 63 normal children); 17 children had moved away and were excluded from the study. In all, 108 letters of invitation were issued, to which 92 families replied. Finally, 75 families participated of whom 41 were from the IUGR group and 34 from the control group. Table 1 shows the comparison between the two groups in relation to the perinatal and current variables.

Medical problems

IUGR children had slightly more medical conditions than the control group (29% *v* 12%, $p = 0.07$). The commonest medical condition was asthma. In the IUGR group two children had autism, one had epilepsy, one had attention deficit hyperactivity disorder and two had unspecified developmental delay.

Comparison of the z score data for weight at birth, final weight, final height and final BMI of the two groups

Multivariable regression models using standard deviation (z) scores confirmed that IUGR children were born lighter and they were shorter and remained lighter at 9 years compared with the

Table 2 Adjusted means for birthweight z score and weight z score, height z score and body mass index (BMI) z score at 9 years for the intrauterine growth restriction (IUGR) and control groups

	IUGR Adjusted mean (95% CI)	Control Adjusted mean (95% CI)	Mean difference (95% CI)	Probability value*
Birth weight	−2.1 (−2.3 to −1.8)	0.2 (−0.2 to 0.5)	2.3 (−2.6 to −1.8)	<0.001
Final weight	−0.4 (−0.7 to −0.1)	0.6 (0.3 to 1.0)	1.0 (−1.5 to −0.5)	<0.001
Final height	−0.5 (−0.7 to −0.2)	0.0 (−0.3 to 0.2)	−0.5 (−0.8 to −0.1)	0.002
Final BMI	−0.2 (−0.5 to 0.1)	0.7 (0.3 to 1.1)	−0.9 (−1.4 to −0.4)	0.002

*Probability values are for general linear model analysis after adjusting for any significant covariates.

control group. Table 2 compares the adjusted z scores of the weights, heights and BMIs of the two groups at birth and at 9 years, and shows that the average birth weight in the IUGR group was more than 2 SD below the mean (z = −2.1) whereas the average birth weight of the control group was just above the mean (z = 0.2). At the age of 9 years the average weight of the IUGR group was 0.4 SD below the mean (z = −0.4) and the average weight of the control group was 0.6 SD above the mean (z = 0.6). The average height at the age of 9 years for the IUGR group was 0.5 SD below the mean (z = −0.5) whereas the corresponding value for the control group was on the mean (z = 0.0). The average BMI z-score for the IUGR group at 9 years of age was just below the mean (z = −0.2) whereas the corresponding value for the control group was 0.7 SD (z = 0.7) above the mean. All these differences were highly significant.

Comparison of change in weight z score between birth and 9 years in the two groups

The change in weight z score variable measured changes in the position of weight between birth and 9 years relative to the mean weight of the 1990 reference population. A positive value indicated that the weight has moved upwards in the centile chart whereas a negative value meant that the weight has fallen down in the centile chart. Table 3 shows the comparison between the two groups in relation to change of weight z score between birth and 9 years. At the age of 1 year the average weight of the IUGR group increased by 0.9 SD compared with an increase of 0.3 SD for the control group. At the age of 2 years the average weight of the IUGR group increased by 1.2 SD compared with an increase of 0.3 SD for the control group. At the age of final measurement the average weight of the IUGR group increased since birth by 1.5 SD compared with an increase of 0.4 SD for the control group.

Although the available weight measurements were fewer, the trend of rapid weight gain in IUGR children was present in the early years. Weight measurements of 53 children were available at 1 year and at 2 years of age. The rate of weight gain seemed to be more pronounced during the second year of life for the IUGR children. Thereafter the increase in z score changes slowed down considerably. The children in the IUGR group were lighter at birth and despite having a higher rate of weight gain they remained lighter than the control group by the age of 9. Between birth and 9 years of age the IUGR group increased their z score by 1 SD more than the control group, but at 9 years of age they remained 1 SD behind the control group.

Within each group there was no correlation between initial score and final score, so regression to the mean (RTM) had already occurred within each group. When the data for birthweight z scores were ranked within each group, it became apparent that the initial z score has no significant predictive value concerning the final z score. The change of weight z score for each group exceeded that expected under RTM and was present even after adjustment for birthweight z score.

Determinants of birthweight z score, final weight z score, final height z score, final BMI z score and change of weight z score obtained by multivariable statistical analysis

We used univariable analyses to narrow the selection process by eliminating variables with a probability >0.1 of predicting each dependent variable. Then the remaining variables were entered into a multivariable main effects model, and significant interactions were explored. The stepwise method was also used to reach the final model. Results of the multivariable analysis (table 4) showed that IUGR was the only common significant predictor for all the outcome measurements. Paternal and maternal heights were additional significant predictors for final height z score. For the change of weight z score there was a main effect of IUGR, and interactions between using medication and maternal height, and interaction between using

Table 3 Change of weight z score from birth to 9 years in the intrauterine growth restriction (IUGR) and control groups

Group	Change in weight z score between birth and 1 year Mean (95% CI)*	Change in weight z score between birth and 2 years Mean (95% CI)*	Change in weight z score between birth and 9 years Mean (95% CI)	Correlation between birth weight z score and weight z score at 9 years (pr)
IUGR	0.9 (0.3 to 1.4)	1.2 (0.7 to 1.6)	1.5 (1.2 to 1.9)	0.10 (0.52)
Control	0.3 (−0.1 to 0.7)	0.3 (−0.2 to 0.8)	0.4 (−0.01 to 0.8)	0.13 (0.48)
Difference between changes in mean z scores between the two groups	0.6	0.9	1.1	
Probability	p = 0.1	p = 0.01	p = 0.001	

Probability values are for general linear model analyses after adjusting for any significant covariates.
IUGR children gained weight at a faster rate compared with the control group and the difference in the rate of weight gain was present from an early age.
*Measurements were available for 53 children.

Table 4 Multivariable statistical analysis for birthweight z score, final weight z score, final height z score, final body mass index (BMI) z score and change of weight z score

Significant predictor(s)	z Score: Birth weight	Final weight	Final BMI	Final height	Change of weight between birth and 9 years
IUGR	Yes (p<0.001)	Yes (p<0.001)	Yes (p = 0.017)	Yes (p<0.002)	Yes (p<0.001)
Birth weight	No	No	No	No	Yes (p = 0.001)
Paternal height	No	No	No	Yes (p = 0.017)	No
Maternal height	No	No	No	Yes (p = 0.04)	No

medication and having been breast fed, were also significant (p = 0.013 and p = 0.027, respectively). The number of children involved in some of the interactions were relatively small thus making the interpretation difficult. Birth weight was not a significant predictor of final weight z score.

For change in weight z score competing models were set up, comparing birth weight and IUGR. The birthweight model accounted for 59.5% of the variability in the data, considerably more than the model which featured IUGR rather than birth weight (37.7%). However when they were included in the same model IUGR did not significantly predict change in weight z score between birth and 9 years over and above birth weight (p = 0.205 for IUGR) but birth weight remained significant (p<0.001). Thus it may be concluded that the best predictor of change in weight z score between birth and 9 years in the current sample was weight at birth rather than membership or not of the IUGR group. However, we included the results from a model including IUGR and not birth weight because the principal aim of the research was to compare the IUGR group with the control group. IUGR probably predicted change in weight z score because of its high correlation with birth weight (r = 0.74, p<0.001, tolerance 0.45).

Table 5 shows the overall comparison of body size, where at least half of the control group was above the 85th centile for BMI and 23% above the 95th centile—that is, there was a greater tendency to obesity in the control group.

DISCUSSION

By any criterion, our growth-restricted infants did not fully ''catch up'' with our control group of infants in height, weight or body stature by the age of 9 years and as a result were substantially smaller and lighter and may well remain so throughout life. Clearly the impact of malnutrition in utero extends at least into early childhood and beyond, and it is a most powerful influence on the growth process. Birth weight on its own had a weak influence on later body size or weight, although it was a good predictor of change in z score for weight. If it can be construed that changes in weight z scores imply rate of growth, then the growth-restricted infants grew faster than normal children, while remaining smaller in actual weight throughout. It remains to be seen whether at puberty the difference in size can be reduced by the growth spurt. From the evidence presented in this paper that seems unlikely.

Obesity has been predicted in IUGR infants as a consequence of early overfeeding and may be the basis of a general increase in morbidity and particularly premature cardiovascular diseases in adults.[1 5] We have shown that the tendency to obesity was more likely in the normal group of children, which is in keeping with the widely reported increase in the incidence of obesity in young children in affluent Western societies, and is undoubtedly nutritionally related.[7–9]

In our study there were generally more illnesses in the IUGR group, mainly wheezing and asthmatic illnesses, and surprisingly, two cases of autism. All the usual factors reported to be related to smallness at birth were overwhelmingly present in these IUGR infants—for example, low socioeconomic status and maternal smoking—and they continued to be present during the remainder of early childhood. So great are the influences of intrauterine conditions on the developing fetus that they are not easily reversed when normal nutrition is restored. Although the parental heights of the IUGR children did not differ from those of the parents of our control group, there was an overall relationship between parental heights and the height at 9 years of age generally. This suggests that final height is largely genetically determined and environmental factors, unless extreme, are perhaps not as important. Similar smallness and stunting in IUGR children have been shown in Guatemalan, Finnish and South African children, in spite of the use of different measuring techniques and analytical methods.[2 4 10–12] However, Adair showed marked compensatory growth in Filipino children, using change of height z scores.[13]

Table 5 Body mass index (BMI) centile data at the age of 9 years in both study groups

	IUGR (n = 41)	Control (n = 34)
BMI centile (mean, median)	47.32, 47.94	71.18, 83.44
Children above the 85th centile for BMI (n (%))	5 (12)	17 (50)
Children above the 95th centile for BMI (n (%))	3 (7)	8 (23.5)

What is already known on this topic

- Fetal growth restriction can influence subsequent body size.
- There is conflicting evidence that intrauterine growth restriction leads to obesity in later life.

What this study adds

- Children with fetal growth restriction gain weight at a much faster rate but do not fully catch up by the age of 9 years with normal children.
- There is no evidence that fetal growth restriction is associated with later obesity.

The similarity of growth pattern in groups so diverse in culture, nutrition and socioeconomic status is testimony to the widespread nature of intrauterine malnutrition and the irreversibility of its impact. That obesity can be detected in normal 9-year-old children may be a sign of poor early nutrition, coupled with a predisposition from early childhood or even in utero, an effect opposite to that of fetal growth restriction. The importance of the detection of obesity in early childhood can now be measured by its impact on the cardiovascular system.

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Authors' affiliations

Supratik Chakraborty, Desaline Veronica Joseph, Michael John Gordon Bankart, Department of Health Sciences, University of Leicester, Leicester, UK
Stewart A Petersen, Department of Medical Education, University of Leicester, Leicester, UK
Michael P Wailoo, Department of Health Sciences, University of Leicester, Leicester, UK

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