ORIGINAL ARTICLE

Postnatal factors associated with failure to thrive in term infants in the Avon Longitudinal Study of Parents and Children

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Arch Dis Child 2007;**92**:115–119. doi: 10.1136/adc.2005.091496

Supplemental appendices are available at <http://adc.bmj.com/supplemental>

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Accepted 7 August 2006
Published Online First
11 August 2006

Failure to thrive (FTT) is a term used to describe children whose growth is relatively poor in infancy,¹ and is associated with deficits in development and social interaction. As the most objective clinical finding associated with the condition of FTT is poor weight gain,² the term "growth faltering" is preferable for these infants as it avoids the pejorative use of the word "failure".

In the complex literature on FTT, many factors have been reported to be associated with the condition,³ including biological factors such as parental size,⁴ social factors including deprivation, maternal educational level and family size,⁵ and a wide range of physical conditions.⁶ In most cases, the final pathway is nutritional intake inadequate for the metabolic and growth needs of the child. However, although there is a large literature on the factors associated with FTT,³ many of the studies are limited as a result of small sample size, being hospital or clinic based, or using retrospective data—and the research field is plagued by diagnostic inconsistency between studies.¹ The Avon Longitudinal Study of Parents and Children (ALSPAC; <http://www.alspac.bristol.ac.uk>) provides a unique opportunity to investigate FTT in a whole population of infants, using prospectively collected information. We have already described the familial, social and prenatal factors associated with FTT in this cohort,⁴ and now report on the postnatal factors associated with poor infant growth.

METHODS

All births to women resident in the former Avon Health Authority area, with an expected date of delivery between 1 April 1991 and 31 December 1992, were eligible for enrolment in ALSPAC; >80% of the known births from the geographically defined catchment area were included, resulting in a total cohort of 14 062 live births. This study population has social

Objective: To assess the contribution of postnatal factors to failure to thrive in infancy.

Methods: 11 900 infants from the Avon Longitudinal Study of Parents and Children (ALSPAC), born at 37–41 weeks' gestation, without major malformations and with a complete set of weight measurements in infancy (83% of the original ALSPAC birth cohort) were studied. Conditional weight gain was calculated for the periods from birth to 8 weeks and 8 weeks to 9 months. Cases of growth faltering were defined as those infants with a conditional weight gain below the 5th centile.

Results: Analysis yielded 528 cases of growth faltering from birth to 8 weeks and 495 cases from 8 weeks to 9 months. In multivariable analysis, maternal factors predicting poor infant growth were height <160 cm and age >32 years. Growth faltering between birth and 8 weeks was associated with infant sucking problems regardless of the type of milk, and with infant illness. After 8 weeks of age, the most important postnatal influences on growth were the efficiency of feeding, the ability to successfully take solids and the duration of breast feeding.

Conclusions: The most important postnatal factors associated with growth faltering are the type and efficiency of feeding: no associations were found with social class or parental education. In the first 8 weeks of life, weak sucking is the most important symptom for both breastfed and bottle-fed babies. After 8 weeks, the duration of breast feeding, the quantity of milk taken and difficulties in weaning are the most important influences.

and demographic characteristics in common with those recorded in the UK national census surveys.⁷

Of the 14 062 live births in the study, a small proportion (0.7%) was lost to follow-up mainly because the family moved out of the study region. Infants with major congenital abnormality likely to affect feeding (eg, Down's syndrome, cleft palate; 89/13 970, 0.6%) and infants born before 37 or after 41 completed weeks' gestation (893/13 970, 6.4%) were excluded. We also excluded 1292 infants who had incomplete weight data, resulting in a final sample of 11 900 infants (83% of the original cohort). As typically found in the literature, there were more exclusions among social classes III, IV and V than from social classes I and II (26.6% v 19.1%), but the final sample contained a broad spectrum of social background including many families with limited economic resources.

Weight data were extracted from the Avon Child Health Computer system, using measurements made as part of the local pre-school child health surveillance programme. Measurements were taken at birth, at 8 weeks (range 1–3 months) and at 9 months (range 6–12 months). All weights were standardised to z scores adjusting for differences in sex and age (gestational age in weeks for weight at birth and infant age in weeks for subsequent weights). Growth was assessed by calculating the difference in z scores between two time points and adjusting for regression towards the mean using correlates provided by the British 1990 Growth Reference.^{8,9} This increasingly used technique reflects infant growth more accurately, as it accounts for the smaller infants who tend to grow faster and the larger infants who tend to grow slower. Cases of growth faltering were defined as those infants below the 5th centile for weight gain, corresponding to a conditional

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; FTT, failure to thrive

growth score of -1.645 . Controls were all the other infants in the cohort above the 5th centile. Data on feeding were extracted from questionnaires completed by the infant's parents at the following ages (response rate): antenatal (88%), 4 weeks (87%), 6 months (81%) and 15 months (84%).

Ethical permission for the ALSPAC was granted by the ethics committees of the United Bristol Healthcare Trust, Frenchay and Southmead NHS Trusts and the study was also monitored by the ALSPAC Ethics and Law Advisory Committee.

Statistical methods

Correlation was calculated as Pearson's product moment coefficient for normally distributed data. Odds ratios (ORs), 95% confidence intervals (CIs) and p values (all quoted as two sided) were calculated for both the univariate and multivariate analyses. In the univariate analysis, the significance of differences was determined using the χ^2 test with Yates's continuity correction (or Fisher's exact test when an expected cell count was <5). Variables significant at the 5% level in the univariate analysis were entered into subsequent multivariate models constructed in SAS¹⁰ using the stepwise method for selection of variables, the dependent variable indicating whether the infant was in the slowest growing 5% of the cohort.

RESULTS

The mean (standard deviation (SD)) birth weight of the term infants was 3459 (410) g, with the mean birth weight SD scores for boys and girls close to 0, indicating that the sample was very similar to the UK standard population at birth. Only 2.5% of this term cohort was born <2500 g and classified as low birth weight. We found 528 cases of growth faltering from birth to 8 weeks and 495 cases from 8 weeks to 9 months (table 1).

Birth to 8 weeks

The univariate analysis of maternal and infant factors associated with slow growth in the first 8 weeks showed that infants from older mothers (>32 years, the highest quintile of the age distribution of mothers in the ALSPAC) and shorter mothers (<160 cm, the lowest quintile of mothers' heights) were more likely to be cases of growth faltering. Poor growth was associated with reported feeding problems, and with infant illness or admission to hospital. No significant associations were found with social class or parental education.

The 11 factors significant in the univariate analysis at the 5% level were entered for the multivariate analysis (table 2). Prenatal factors that retained significance were short maternal height, older mothers and lack of private transport. Major postnatal factors identified were difficulty in feeding and infant illness. The feeding symptoms significantly associated with weight faltering were weak sucking and difficulties in feeding, but not vomiting, dribbling or refusing feeds. Weak sucking was equally important in breastfed and bottle-fed infants: one in six infants in the cohort was reported by their parent to have weak sucking, and growth faltering was nearly twice as likely in this group.

8 weeks to 9 months

Of the 528 infants with growth faltering from birth to 8 weeks, only 30 (5.7%) also had poor growth for the second period. No data were available as to what interventions were made for those infants whose growth rate recovered. A similar range of maternal and infant factors was used in univariate analysis for the second period of infancy. Although only 0.6% of the cohort was of Asian origin (Indian subcontinent and Far East combined), growth faltering in the second period was 3–4 times as common in this group, which had a similar mean weight z score (-0.66) at birth, 8 weeks and 9 months. Other associated maternal factors were height and parity, but not age or educational attainment.

The median duration of breast feeding was 4 (interquartile range 1.5–8.5) months: 28% of infants were breast fed for >6 months, and 15% were breast fed for the whole 9-month period under study (fig 1). The mothers who breast fed for ≥ 9 months tended to belong to a higher social class and were less likely to be smokers. Infants who were breast fed for ≤ 9 months were born to larger families, were reported to have more difficulty in accepting solids and were more likely to refuse other milks (table 3).

Most infants in the study were weaned between 4 and 6 months, and those infants who received ≤ 2 solid meals/day at 6 months were more likely to be cases of growth faltering than controls.

In contrast with the earlier growth period, infant illness was not associated with growth faltering between 8 weeks and 9 months. No associations were found with measures of social class or parental education.

Table 1 Characteristics of infants with growth faltering (z score <-1.645)

	Birth to 8 weeks		8 weeks to 9 months	
	Case	Control	Case	Control
n	528	11900	495	11223
Cohort (%)	4.5	95.5	4.2	95.8
Time between measurements (days)	56 (49–62)	55 (46–60)	226 (215–241)	225 (213–240)
Median (IQR)				
Birth weight (g)	3440 (3120–3768)	3460 (3160–3770)	3320 (3000–3660)	3460 (3160–3770)
Median (IQR)				
Weight z score at birth*	+0.07 (1.14)	+0.07 (1.00)	+0.02 (1.01)	+0.07 (1.00)
Mean (SD)				
Weight z score at 8 weeks†	-1.55 (0.83)	+0.10 (0.92)	-0.17 (1.02)	+0.04 (0.97)
Mean (SD)				
Weight z score at 9 months‡ Mean (SD)	–	–	-1.74 (0.74)	+0.24 (0.98)
Growth z score from birth to 8 weeks§	-2.12 (0.45)	+0.08 (0.85)	–	–
Mean (SD)				
Growth z score from 8 weeks to 9 m¶ Mean (SD)	–	–	-2.12 (0.49)	+0.29 (1.02)

IQR, interquartile range.

*Birth weight adjusted for sex and gestational age.

†Weight at age around 8 weeks, adjusted for sex and gestational age.

‡Weight at age around 9 months, adjusted for sex and gestational age.

§Difference in weight z score from birth to 8 weeks, adjusted for regression towards the mean.

¶Difference in weight z score from 8 weeks to 9 months, adjusted for regression towards the mean.

Table 2 Multivariable model of poor weight gain from birth to 8 weeks

		Case		Control		OR (95% CI)	p Value
Criteria		n/N	%	n/N	%		
Parental characteristics (non-reference group)							
Maternal height	<160 cm	142/473	30.0	2300/10027	22.9	1.41 (1.12 to 1.77)	0.004
Maternal age	>32 years	123/528	23.3	2035/11190	18.2	1.40 (1.10 to 1.79)	0.007
Use of a car	None	96/519	18.5	1499/11056	13.6	1.52 (1.09 to 2.13)	0.01
Infant problems (non-reference group)							
Weak sucking at 4 weeks	Yes	151/503	30.0	1601/10791	14.8	2.20 (1.74 to 2.78)	<0.001
Difficult to feed at 4 weeks	Yes	105/525	20.0	1138/11142	10.2	1.52 (1.16 to 2.00)	0.003
Infant health up to 8 weeks	Minor illness	196/528	37.1	3467/11190	31.0	1.43 (1.15 to 1.78)	0.001
	Quite ill or very ill	27/528	5.1	268/11190	2.4	2.08 (1.31 to 3.31)	0.002

n, proportion positive for the criterion; N, total population.

This model included 74.3% of the cohort and was adjusted for the time between measurement of weight from birth to 6–8 weeks.

Other factors looked at in the univariate analysis but not significant in the above model included other parental characteristics (social class, education, maternal smoking, parity and maternal ethnicity), infant characteristics (sex, birth weight, birth centile, multiple births, admission to neonatal intensive care unit and attempted breast feeding in the first 24 h) and other infant problems with feeding (feeding on demand, dribbling milk, slow feeding, small quantities taken, infant dissatisfaction, refusing milk and diarrhoea).

The 12 factors identified in the univariate analysis to be significantly associated at the 5% level with growth faltering during this period were entered for multivariate analysis (table 4).

Distinctive maternal factors in the final model were ethnicity (Asian), height and parity. Distinctive infant factors were breast feeding after 6 months, feeding slowly, and taking small quantity of solids at 6 months.

DISCUSSION

We investigated the factors associated with weight gain in infancy by using a large representative sample from the UK population: the results suggest that the feeding characteristics of the infant are the dominant factors, rather than the socioeconomic status or the educational attainment of the mother. The strengths of the study are the use of a large well-characterised representative sample and prospectively collected feeding data, avoiding many of the methodological weaknesses of hospital and clinic-based samples and of retrospective data collection. The study is limited by the feeding data being derived from maternal report at the time of an ALSPAC questionnaire (4 weeks, 6 months and 15 months), whereas the weight data were collected at routine health service contacts (birth, 8 weeks and 9 months).

In the first 8 weeks, maternal age and height had an influence on early growth, but infant feeding difficulties were important, particularly weak sucking. There may be two underlying explanations for this association: oral–motor dysfunction^{11–13} or differences in the infant's appetite.^{14–15} After age 8 weeks, weight gain was also related to maternal height, and the over-

representation of Asian infants in the slowest growing 5% is also probably a consequence of shorter mothers (but could be a reflection of different infant feeding practices). The most important postnatal influences on growth were the efficiency in feeding, ability to successfully take solids and duration of breast feeding. Although these symptoms were reported by parents, who also influenced the timing of weaning, our results are consistent with behavioural studies¹⁵ reporting that children with FTT are fed as much and as frequently as controls but tend to refuse or reject offered food more often. An alternative explanation is that mothers may sense that the infant is not ready to wean (eg, not demanding solids, or showing immature oral–motor skills when offered tastes of solid food), and they continue to breast feed.

Observational studies have generally shown an association between prolonged breast feeding and slower weight gain.¹⁶ Evidence from the only relevant randomised controlled trial on breast feeding¹⁷ suggests that infants with lower appetites grow more slowly and hence are satisfied with breast milk for longer. However, it is debatable if such slow-growing breast-fed infants are at an overall disadvantage over the life course,¹⁸ as slow growth during infancy may actually have a long-term beneficial effect on reducing the risk of obesity and cardiovascular disease in adulthood.¹⁹

These results have several implications for clinical practice: firstly, a reminder that the early onset and persistence of slow or difficult feeding may be a warning of inadequate nutritional intake and possible growth faltering; and secondly, the importance of supporting parents in weaning their infants at

Figure 1 Proportion of infants with growth faltering from 8 weeks to 9 months (with 95% CI) and duration of breast feeding.

Table 3 Relationships between breast feeding beyond 6 months and reported feeding problems

	Breast fed >6 months*		Rest of cohort		OR (95% CI)	p Value
	n/N	%	n/N	%		
Started lumps early	784/2639	29.7	2313/6662	34.7	0.79 (0.72 to 0.88)	<0.001
≤2 solid meals/day	315/2647	11.9	677/6422	10.5	1.15 (0.99 to 1.32)	0.06
Slow feeding	572/2613	21.9	2106/6257	33.1	0.57 (0.51 to 0.63)	<0.001
Quantities taken too small	872/2601	33.5	2204/6295	35.0	0.94 (0.85 to 1.03)	0.19
Refusing other milk†	966/2713	35.6	846/6844	12.4	3.92 (3.52 to 4.37)	<0.001
Refusing solids	731/2600	28.1	1267/6305	20.1	1.56 (1.40 to 1.73)	<0.0001
No established routine	456/2655	17.2	810/6459	12.5	1.45 (1.27 to 1.64)	<0.001
Infant difficult to feed	914/2623	34.8	2199/6406	34.3	1.02 (0.93 to 1.13)	0.66

n, proportion positive for the criterion; N, total population.

*We have data for breastfeeding duration data on 9557 (81.6%) mothers: of these 2713 (28%) were still breast feeding after 6 months.

†30% of data missing: these infants were put in the reference group, yielding a conservative estimate for this factor.

an appropriate time developmentally. The World Health Organisation (<http://www.who.int/child-adolescent-health>) now recommends that mothers should be encouraged to exclusively breast feed and postpone the introduction of solids until age 6 months. However, the developmental “window” to wean on to solids is short: previous work from ALSPAC^{20, 21} has shown that infants unable to take lumpy solids at 9 months were more likely to have continuing feeding difficulties and poor weight gain in the second year of life. Infants who are still predominately breast feeding at age 9 months are likely to have smaller appetites and may have difficulties taking solids; these infants require careful assessment and their mothers need sensitive support to persist in offering weaning foods of appropriate consistency and variety.

Further research using this longitudinal study will clarify whether early feeding problems leading to growth faltering is a marker for persisting neurological abnormalities and whether it is associated with developmental difficulties later in childhood.

ACKNOWLEDGEMENTS

We thank all the families who took part, the midwives for helping in their recruitment and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. Sue Bonnell and Colin Steer made specific contributions to handling these data.

What is already known on this topic

- Failure to thrive is a term widely used to describe infants whose growth is relatively poor.
- Most research on the topic has been based on samples derived from hospital clinics using data collected retrospectively.

What this study adds

- Factors associated with failure to thrive included sucking problems in the first few weeks, difficulties in weaning on to solids at age 6 months and reliance on breast feeding to ≥9 months. No associations were found with markers of social class and parental education.
- This study challenges the perception that failure to thrive is usually a reflection of social deprivation or neglect, and implies that early feeding difficulties, as a marker of subtle neurological impairment or poor appetite, are the precursors of subsequent poor weight gain.

Table 4 Multivariate model of poor weight gain from 8 weeks to 9 months

		Case		Control		OR (95% CI)	p Value
Criteria		n/N	%	n/N	%		
Parental characteristics (non-reference group)							
Maternal height	(<160 cm)	145/423	34.3	2298/10077	22.8	1.75 (1.37 to 2.23)	<0.001
Parity	>3	128/455	28.1	2100/10497	20.0	1.33 (1.03 to 1.73)	0.03
Ethnicity of mother*	Asian	11/437	2.5	50/10161	0.5	3.09 (1.03 to 9.33)	0.045
Infant characteristics (non-reference group)							
Breastfeeding duration†	>6 months	193/393	49.1	2520/9164	27.5	2.54 (2.01 to 3.21)	<0.001
Infant problems (non-reference group)							
Small feeds	Quantities too small	176/403	43.7	3223/8439	34.1	1.53 (1.22 to 1.91)	0.001
Refusing non-breast milk	Yes‡	129/495	26.1	1847/11223	16.5	1.57 (1.22 to 2.01)	0.001
Baby's health§	Quite ill or very ill	20/495	4.0	267/11223	2.4	1.70 (1.01 to 2.85)	0.047

This model included 69.5% of the cohort.

n, proportion positive for the criterion; N, total population.

*As “Asian mothers” was the only significant category, the reference group was the rest of the cohort.

†As breast feeding at 7–9 months and after 9 months were the only significant categories, these were added together; the reference group was the rest of the cohort.

‡30% of data missing: these infants were put in the reference group, yielding a conservative estimate for this factor.

§As minor illness was not a significant group in the univariate analysis, this was added to the reference group.

Other factors considered in the univariate analysis but not significant in the multivariate model included other parental characteristics (maternal age, social class, education, use of a car, maternal smoking, parity and belonging to other ethnic groups), other infant characteristics (sex, birth weight, birth centile, multiple births and admission to neonatal intensive care unit) and other infant problems with feeding (age started solids, number of solid meals a day, refusing solids, infant difficult to feed, feeding too slowly, no established feeding routine, diarrhoea and hospital admissions).

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Funding: This study was funded by the Wellcome Trust, London, UK (Grant 59579). The UK Medical Research Council, the Wellcome Trust and the University of Bristol provide core support for ALSPAC. All researchers on this study are independent from the funding body.

Competing interests: None.

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ARCHIVIST

The Loeys–Dietz syndrome

The Loeys–Dietz* syndrome was first described in 2005 as an autosomal dominant syndrome (OMIM number 609192). It is characterised by aortic and peripheral aneurysms and arterial tortuosity, bifid uvula and/or cleft palate, and hypertelorism, and is caused by mutations in the genes for the transforming growth factor β receptors 1 or 2 (*TGFBR1* at chromosome 9q33–q34 or *TGFBR2* at chromosome 3p22).

The syndrome was first described in 10 families and is now found in an additional 42 families (Bart L Loeys and colleagues. *N Engl J Med* 2006;**355**: 788–98; see also editorial, *ibid*: 841–4). Of the 52 probands, 40 had all the features of the Loeys–Dietz syndrome and were categorised as having Loeys–Dietz syndrome type 1. Twelve were discovered on genetic screening of 40 patients who had a clinical diagnosis of vascular Ehlers–Danlos syndrome but did not have either the type III collagen abnormalities of Ehlers–Danlos syndrome or the craniofacial features of the Loeys–Dietz syndrome, although some had a bifid uvula. These 12 probands were categorised as having Loeys–Dietz syndrome type II. Of the 30 new probands with the type I syndrome, 21 had mutations in the *TGFBR2* gene and 9 in the *TGFBR1* gene; of the 12 with type II syndrome, 8 had *TGFBR2* and 4 had *TGFBR1* mutations. The phenotypes were similar for mutations in either gene.

The clinical features of the 40 probands with type I syndrome included aortic root aneurysm (98%), arterial tortuosity (84%), other aneurysms (52%), hypertelorism (90%), cleft palate or abnormal uvula (90%), other craniofacial features including craniosynostosis (48%) and blue sclerae (40%), and skeletal abnormalities including arachnodactyly (70%), pectus deformity (68%) and joint laxity (68%). Less common features included developmental delay, hydrocephalus and Arnold–Chiari malformation. The clinical features of type II Loeys–Dietz syndrome were those of vascular Ehlers–Danlos syndrome. Twelve women (5 with type I and 7 with type II syndrome) had 21 pregnancies, and 6 (1 with type I and 5 with type II) had major complications (aortic dissection in 4, uterine rupture in 2). Among 52 probands and 38 relatives with Loeys–Dietz syndrome, 27 died before or during the study period. The main causes of death were dissection of the thoracic or abdominal aorta, and the mean age at death was 26 (range 0.5–47) years. The mean age at death was lower in those with type I (22.6 v 31.8 years), and patients with more severe craniofacial features had earlier onset of cardiovascular events.

The differential diagnosis of Loeys–Dietz syndrome includes atypical Marfan syndrome, vascular Ehlers–Danlos syndrome, and familial thoracic aortic aneurysm and dissection. Genotyping of *TGFBR* may be needed to make the diagnosis. Animal research has led to the suggestion that TGF β antagonists such as the angiotensin II type 1 receptor antagonist, losartan, might be beneficial in these syndromes and even in diabetic vascular disease. A trial of losartan versus β -blockers in young people with Marfan syndrome and aortic aneurysms is in its early stages.

* Dr Bart L Loeys works at the Centre for Medical Genetics in Ghent, Belgium and Dr Harry C Dietz at the Johns Hopkins Hospital in Baltimore, USA.