Growth Faltering in Low-Income Countries

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Abstract

Meta-analysis of growth data from over 50 low and low-middle income countries shows a consistent pattern of stunting and poor weight gain from about 3 months of age and persisting until at least 5 years. Children tend not to be wasted because their short stature offsets their underweight, leading to a rather adequately proportioned appearance. This frequently conceals the true levels of malnutrition in communities. At the macro-environmental level such growth faltering is due to the combined effects of poverty, food insecurity, low-dietary diversity, a highly infectious environment, poor washing facilities and poor understanding of the principles of nutrition and hygiene. These tend to be ameliorated as communities pass through the demographic transition with improved incomes and education. Because such changes will take generations to achieve, the global health community continues to search for effective interim solutions. Disappointingly, apart from intensive feeding programmes aimed at rehabilitating severely malnourished children, there are few examples of very successful nutrition interventions. This emphasizes the need for a better understanding of the etiology of growth failure. This paper uses anthropometric data collected over 6 decades in subsistence-farming communities from rural Gambia to illustrate the typical key features of growth faltering. Arising from this analysis, and from gaps in the published literature, the following issues are highlighted as still requiring a better resolution: (1) the pre-natal and inter-generational influences on growth failure; (2) the ontogeny of the infant immune system; (3) the exact nature of the precipitating insults that initiate gastroenteropathy; (4) the effects of both enteric and systemic infections on the hormonal regulation of growth; (5) interactions between macro- and micro-nutrient deficiencies and infections in causing growth failure, and (6) the role of the microbiome in modulating dietary influences on health and growth.

More than a decade ago Shrimpton et al. [1] summarized growth data from demographic studies across 54 low- and low-to-middle income countries, an analysis that was recently updated by Victora et al. [2]. The key messages from these analyses are that such children are born small and then growth faltering, especially in length/height, starts soon after birth and continues for the first 2 years of life leaving children in such environments averaging about −1.0 z-scores for weight and −1.75 z-scores for
height against Western reference curves from 2 years onwards. Weight-for-height is not appreciably diminished leaving such children with a relatively normal appearance that underscores the importance of assessing height. Most disturbingly, these statistics have barely shifted in the decade between the two summaries. It is these analyses that form the basis of the current emphasis on the ‘first 1,000 days’ (i.e. the 280 days of pregnancy plus the first 730 days of post-natal life). It is widely stated that this is the critical period in which interventions must be delivered and that later recovery is not possible. There is some validity to this claim but, as we will demonstrate below, it is far from absolute and requires a more nuanced interpretation than is currently applied.

This paper will use anthropometric data collected over 6 decades in subsistence farming communities in rural Gambia to provide a more fine-grained analysis of life-course patterns of growth faltering and to set out some key remaining challenges to our understanding of these key health-determining patterns of poor growth.

**Poor Growth in Rural Gambia**

Figure 1a illustrates the early growth trajectories of a random sample of 120 rural Gambian babies studied longitudinally [3] and plotted against the UK 1990 Growth Charts in order to best describe the differences against what might be considered an optimal growth pattern [4]. As is typical for this environment they were born small, showed very impressive catch-up in the first 3 months of postnatal life (when exclusively breast-fed and hence greatly protected from infections), and then showed serious growth faltering for the remainder of infancy. Contrary to the Shrimpton and Victora analyses [1, 2], which are heavily influenced by the extreme stunting that occurs in many South-East Asian countries, there is greater weight loss (down to −1.8 z-scores) than height loss (down to −1.2 z-scores) and consequently weight-for-height (illustrated here as BMI) is greatly affected (down to −1.5 z-scores). The deficit in head circumference (down to −2.25 z-scores) is the most concerning given the strong relationship between this dimension and brain size, and may have significant implications for the development of the human capital of poor nations. It must be noted, however, that the UK 1990 head circumference values are considerably higher than the new WHO Standards [5].

**Secular Trends in Growth Faltering in Rural Gambia**

The MRC International Nutrition Group’s studies in rural Gambia are unique in having accurate demographic and anthropometric data stretching back over 6 decades. Figures 1b–d illustrate that, despite making huge progress in saving lives (with greater than 8-fold reductions in under 5 years mortality [6]) and in reducing
the prevalence of diarrhoea [7] and other infections, our presence in these communities, and by inference the numerous intervention strategies that we have trialed, have had a much less pronounced impact on growth. A recent analysis of children's anthropometry according to the socio-economic status and living conditions of their parents, and including MRC staff members, concluded with the salutary observation that there is a very high threshold of development that needs to be attained before a significant impact on growth is observed [8]. This evidence suggests that the multiple stressors that precipitate growth faltering all need to be ameliorated simultaneously to achieve healthy growth; a conclusion that is in synchrony with current trials of combined nutrition and water, sanitation and hygiene (WASH) interventions.

Fig. 1. Contemporary growth patterns of rural Gambian children and secular trends over 6 decades.  

- Mean (±SE) anthropometric z-scores against the UK1990 Growth Reference Curves to illustrate the disparity against a European population (n = 120).
- Mean (±95% CI) anthropometric z-scores calculated against the WHO Child Growth Curves averaged to mid-decade since the 1950s (n = 7,829 with much larger numbers in the later decades due to higher survival rates and population growth). 

HAZ = Height-for-age z-score; WAZ = weight-for-age z-score; WHZ = weight-for-height z-score.
A Longer ‘Life-Course’ View of Growth Faltering

The current emphasis on the ‘first 1,000 days’ provides a useful rallying point around which to focus political momentum for change, but as a scientific concept it is naive and potentially misleading. First, it implicitly ignores the self-evident truth that the pre-conceptional nutritional status and physical size of a mother has an immense impact on her offspring’s size and growth, and that such effects therefore span multiple generations. Second, it uses only cross-sectional data covering the first 5 years of life to conclude that growth deficits, once incurred, cannot be recovered.

Our data from rural Gambia tell a substantially different story as illustrated in figure 2. Figure 2a shows the smoothed height curves to 30 years of age for females (males show very similar patterns and the weight curves are also similar). Each subject contributes multiple data points thus providing a mixed longitudinal and cross-sectional analysis. Figure 2b identifies six somewhat discrete phases of growth and a seventh apparent phase that is an artifact caused by using a non-Gambian reference population. Phase 1 represents in utero growth failure; more severe for birthweight than birthlength in this population. Phase 2 shows the precipitate decline in height during the first 2 years that is typical of such populations. Phase 3 is not described in the Shrimpton/Victora analyses [1, 2] and represents a very significant recovery of about 0.75 z-scores between 2 and 5 years of life. We interpret this as a period during which the children’s immune systems have learnt to cope with the multiple infectious threats and when acute infections are less frequent thus allowing a greater nutrient acquisition and tissue deposition. During phase 4a in later childhood growth runs parallel to the reference curves. The apparent faltering in phase 4b is a statistical artifact caused by the fact that the reference populations enter puberty earlier than the Gambians. Phase 5 represents the (somewhat delayed) pubertal growth spurt that, in these populations, is notable for its long duration with full adult height only being obtained at close to 20 years (even later in boys). During this phase the initial (artifactual) decline of phase 4b is recovered and, most importantly, there is a further catch-up of almost 1 z-score before girls enter adulthood (phase 6). The horizontal lines in figure 2c show that, even in the absence of nutritional interventions, there has been a height catch-up of around 1.5 z-scores between the 2 years nadir and adulthood; an observation that underscores the need to re-evaluate the current tenet that recovery is not possible after the first 1,000 days.

Importance of Inter-Generational and Fetal Programming of Growth Faltering

There is a rapidly expanding knowledge base in support of the concept that human growth in any generation is modulated by the epigenetically imprinted history of the nutritional exposures of prior generations [9]. This may be particularly crucial for in utero growth because maternal body size has an effect in addition to epigenetic
Inheritance. Data from animal models suggests that the majority of such effects are passed through the female line [10]; human data generally, but not exclusively, supports this. We have recently demonstrated that the epigenome of neonates and infants is affected by the pre- and peri-conceptional nutritional status of a mother [11–13], but whether these epigenetic modifications translate into effects on growth is not yet known.

In figure 3, we compare the postnatal growth trajectories of Gambian children defined as extreme positive (top 10%) and negative (bottom 10%) growth deviants compared to their contemporary peers and defined in three ways: figure 3a shows

**Fig. 2.** Life-course variations in mean height-for-age z-scores from neonates to adults in rural Gambians. **a** Mean height-for-age z-scores calculated from 19,486 measurements covering the periods 1950–1980. **b** The 6 identifiably discrete phases of growth delineated (see main text for narrative). **c** The degree of catch-up attained between the growth nadir at 2–3 years of age and adulthood.
the growth patterns of children selected as the tallest and shortest 10% at birth, figure 3b shows the longitudinal growth patterns of children selected as positive and negative growth deviants at age 2 years (the time of worst attained growth in this community and in poor populations worldwide), and figure 3c shows the positive and negative deviants defined according to the most extreme 10% of centile crossing between birth and 2 years. These graphs clearly illustrate some key features of childhood growth faltering. First, that at 2 years of age the top and bottom 10% of children according to attained height are separated by 4 z-scores showing that the variance in growth in this population is far greater than in the UK 1990 reference children (presumably because of the growth dispersing effects of infections). Second, that the antecedent growth curves of these groups show that they were already separated by 2 z-scores at birth (fig. 3b) confirming the importance of poor fetal growth as a contributory factor in postnatal growth faltering. Third, that when selected according to positive and negative deviance at birth (fig. 3a) there is some tendency towards catch-up and catch-down, but the groups remain largely discrete by 2 years of age. And finally, that there is a small number of children who show postnatal growth trajectories (fig. 3c) that cross-centiles (both upwards and downwards) in a pronounced way. This mode of selection, by definition, selects out small babies showing the greatest catch-up and large babies showing the greatest faltering.

Detailed studies concentrating on defining the causes of these different patterns of positive and negative growth deviance should provide a particularly powerful method for defining causal pathways. We summarise in the next section some of the key outstanding research areas the resolution of which we believe would accelerate the development of novel growth-promoting interventions.

Key Research Gaps Regarding the Aetiology of Growth Faltering in Low-Income Countries

Arising from the analysis briefly presented above, from gaps in the published literature, and from the many intervention trials that we have tested in rural Gambia with only modest success in terms of reversing early-childhood growth faltering, the following issues are highlighted as still requiring a better resolution:

The Pre-Natal and Inter-Generational Influences on Growth Failure
There is still much to learn about the regulation of fetal growth by short- and long-term (inter-generational) influences. Fortunately, this is a vibrant research area recently invigorated by large grant calls from the Bill and Melinda Gates Foundation (BMGF) and the Global Alliance for Prevention of Prematurity and Stillbirths (GAPPS), and by widespread enthusiasm for exploring the mechanisms and consequences of nutritional and other influences on the human epigenome. Our own work
in this area is taking a lifecourse approach to studying the continuum of fetal and post-natal growth trajectories as part of a large intervention study; The ENID Trial (ISRCTN 49285450).

The Ontogeny of the Infant Immune System
As the neonate emerges from its essentially sterile environment in utero, it has to adapt to the new challenges of differentiating self from non-self antigens. Under the partial and waning protection of maternally derived specific antibodies and, optimally, under the additional cover of breastfeeding, the infant’s innate immune systems need to be activated and trained, and its adaptive immunity must be primed. Many of the details of these processes remain obscure and further research is required to identify the optimal strategies for immune enhancement by exploiting both the specific and powerful non-specific [14, 15] effects of vaccines and the potential for nutritional enhancement of these effects.

Exact Nature of the Precipitating Insults that Initiate Gastroenteropathy
Research at our centre [e.g. 16, 17] and elsewhere [18] has identified a persistent gastroenteropathy (previously termed tropical enteropathy and now more usually referred to as environmental enteropathy) as being strongly correlated with, and probably on the causal pathway to, early growth failure. The nature of the precipitating and perpetuating insults, and the interactions between environmental enteropathy, mucosal immunity and the effectiveness of oral vaccines, still remains obscure [19] and thus impedes the development of preventive and therapeutic strategies. This topic has also been prioritised by BMGF and is receiving concerted attention that will hopefully yield novel, and therapeutically relevant, insights.

Fig. 3. Early height growth curves for positive and negative growth deviants in rural Gambian children. Growth deviance is defined as the tallest versus the shortest 12.5% of children from a random sample of 200. a Post-natal growth trajectories for the tallest and shortest groups at birth. b Antecedent growth trajectories of the tallest and shortest groups at 2 years of age. c Trajectories of those children who show greatest positive and negative centile crossing between birth and 2 years. Means ± 95% CI (n = 25 for each curve).
**Effects of both Enteric and Systemic Infections on the Hormonal Regulation of Growth**

The study of hormonal regulation of child growth has been based almost exclusively on clinical investigations of children in high-income countries showing clinically aberrant growth. There are surprisingly little data on normal values of growth-modulatory hormones and their promoters, receptors and regulators (e.g. binding proteins) even in high-income settings. There is virtually no systematic data from low and middle-income countries. Because alterations in auxological hormones represent the first (and effector) steps in growth modulation they may provide excellent biomarkers with which to study acutely the growth-promoting and growth-inhibiting influences of various nutritional and infectious scenarios. There are difficulties relating to cost, interpretation (because circulating levels do not necessarily reflect effector status) and the need for repeated blood sampling. Despite these factors this is emphasized as an important area for investment that may yield surprisingly fast returns in terms of exploitable knowledge (for instance in relation to effects of animal vs. nonanimal proteins).

**Interactions between Macro- and Micro-Nutrient Deficiencies and Infections in Causing Growth Failure**

Dietary recommendations for children and, as a consequence, the composition of recommended diets (including linear programming approaches to optimal complementary food formulation), supplements and therapeutic foods (ready-to-use-supplementary foods, etc.) are based on a long-established ‘classic’ set of energy, protein, fat, carbohydrate and (usually) 23 essential micronutrients. Guidelines on protein quality take account of needs for the essential amino acids. Linoleic and linolenic acid are often now included to ensure adequate n–3 and n–6 series precursors for long-chain polyunsaturated fatty acids. Little attention has been paid to other possible growth limiting or conditionally essential nutrients. Choline represents a good example of an essential nutrient that is likely to be low in typical low-income country diets and that may limit physical growth and neurological development [20]. Choline intake of breastfed babies is high but there are little or no data on weanlings. Glycine is an example of a nonessential nutrient which may become conditionally essential in times of stress (such as pregnancy) [21]. The question arises as to whether the efficacy of current multiple-micronutrient-fortified interventions is limited by the omission of ‘nonclassical’ nutrients such as choline or glycine or others to be determined?

**Role of the Microbiome in Modulating Dietary Influences on Health and Growth**

Technological advances in gene sequencing and meta-data processing have fuelled a quantum leap in our understanding of the human microbiome. The application of these methods to the problems of global child health has already yielded fresh insights into the importance of the gut flora in mediating nutritional disease. For instance transplantation into previously germ-free mice of the microbiota from Malawian children
suffering kwashiorkor precipitates significant weight loss when the mice are fed a typical Malawian diet but not when they remain on a standard chow [22]. The Malawian diet alone or microbiome transplantation from a kwashiorkor patient’s unaffected monozygotic twin does not cause weight loss, emphasizing that there is a malign interaction between the two factors, and that much further research will be required to elucidate the details of diet-microbiome interactions in determining child growth.

Conclusions

The science agenda laid out above concerning the etiology of growth faltering in low-income countries will require the concerted and coordinated efforts of numerous research teams. Many of the fundamental questions have remained unaltered for decades but recent research has provided new signposts on the discovery trail, and immense advances in modern technologies offer unprecedented opportunities for breakthroughs that will translate into novel therapeutic interventions.

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References


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