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Critical windows for nutritional interventions against stunting^{1–3}

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ABSTRACT

An analysis of early growth patterns in children from 54 resource-poor countries in Africa and Southeast Asia shows a rapid falloff in the height-for-age *z* score during the first 2 y of life and no recovery until ≥ 5 y of age. This finding has focused attention on the period –9 to 24 mo as a window of opportunity for interventions against stunting and has garnered considerable political backing for investment targeted at the first 1000 d. These important initiatives should not be undermined, but the objective of this study was to counteract the growing impression that interventions outside of this period cannot be effective. We illustrate our arguments using longitudinal data from the Consortium of Health Oriented Research in Transitioning collaboration (Brazil, Guatemala, India, Philippines, and South Africa) and our own cross-sectional and longitudinal growth data from rural Gambia. We show that substantial height catch-up occurs between 24 mo and midchildhood and again between midchildhood and adulthood, even in the absence of any interventions. Longitudinal growth data from rural Gambia also illustrate that an extended pubertal growth phase allows very considerable height recovery, especially in girls during adolescence. In light of the critical importance of maternal stature to her children's health, our arguments are a reminder of the importance of the more comprehensive UNICEF/Sub-Committee on Nutrition Through the Life-Cycle approach. In particular, we argue that adolescence represents an additional window of opportunity during which substantial life cycle and intergenerational effects can be accrued. The regulation of such growth is complex and may be affected by nutritional interventions imposed many years previously. *Am J Clin Nutr* 2013;97:911–8.

INTRODUCTION

Victora et al (1) have published an analysis of early growth in 54 countries; most from low-income settings. Their analysis updates an earlier version by Shrimpton et al (2) and uses the new WHO growth standards (3). A key finding is that, in the poorer regions of Southeast Asia and Africa, height-for-age *z* scores (HAZs)⁴ start with a deficit at birth (–0.75 HAZ for Asia and –0.35 HAZ for Africa) and decline further in the first 2 y of life (by ~ 1.5 HAZ in both settings) before reaching an apparent plateau until 5 y, when the analysis ended (**Figure 1**).

Both the original and the updated analysis have been influential in developing the concept that –9 to 24 mo represents the optimal “window of opportunity” within which growth-promoting nutritional interventions should be focused. This window is also articulated as the first 1000 d and has been eff-

ectively used as a rallying point for global initiatives (eg, *see* www.thousanddays.org). A view has emerged that interventions outside this window are unlikely to have any effects—a view that is being increasingly adopted in many development circles.

Without seeking to undermine the importance of this period (–9 to 24 mo), or to discourage interventions during this critical period, we present here analyses showing that there are other windows of opportunity to address stunting that should not be overlooked and might well offer additional points for intervention. Our arguments are intended to stabilize the pendulum and prevent an excessive swing away from the more comprehensive approach to nutrition-related health interventions captured by the UNICEF/Sub-Committee on Nutrition model Nutrition Through the Life-Cycle (4, 5). In particular, we argue that adolescence represents an additional window during which growth-promoting interventions, possibly initiated years before puberty, might yield substantial life cycle and intergenerational effects. Interventions outside the first 1000 d may also benefit other outcomes, especially cognitive development (6, 7), but these are not the subject of this article.

We base our reasoning on the following arguments: 1) that the cross-sectional ecologic analyses of Shrimpton et al (2) and Victora et al (1) have been overinterpreted in some quarters; 2) that data on the timing of cell proliferative potential of organ systems across the life span do not support the concept of a catch-up window closing at 24 mo; 3) that an analysis of data from various sources shows that catch-up in HAZ occurs after 24 mo in many poor populations, even in the absence of interventions; 4) that an analysis of our own data from rural Gambia confirms this post-24

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⁴ Abbreviations used: COHORTS, Consortium of Health Oriented Research in Transitioning Societies; HAZ, height-for-age *z* score; RCT, randomized controlled trial; WAZ, weight-for-age *z* score.

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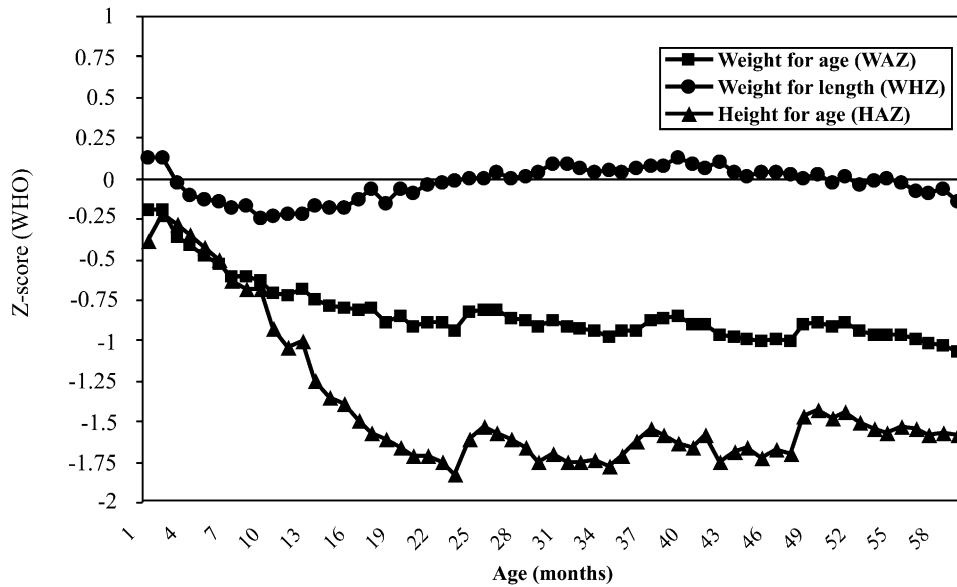


FIGURE 1. Mean anthropometric z scores for 54 studies from low- and middle-income countries relative to the WHO standard. Reproduced with permission from reference 1.

mo catch-up and shows very significant prolonged catch-up growth during adolescence and into young adulthood (again in the absence of interventions); and 5) that, unfortunately, meta-analyses indicate limited efficacy of nutritional interventions between conception and birth and in early postnatal life. Given the importance of maternal stature to reproductive outcomes in the Nutrition Through the Life-Cycle model, we argue that careful studies could be undertaken to explore whether it is feasible, through nutritional interventions, to augment the pubertal catch-up potential of girls while preventing the possible adverse sequelae of early pregnancies, excess weight gain, and/or accelerated closure of growth plates that might reverse the intended effect.

SUMMARY ANALYSES OF NATIONAL DATA ON POSTNATAL GROWTH SHOULD BE INTERPRETED WITH CAUTION

The Shrimpton et al (2) and Victora et al (1) analyses of length/HAZ (the latter reproduced as Figure 1) capture the widely observed fall-off in length growth that occurs in infancy in poor populations and make a very powerful case for focusing interventions on early life. The figure seems to suggest little or no recovery up to the age of 5 y, but must be interpreted with due caution based as they are on an amalgamation of large-scale nationally representative data sets that were not collected for research purposes. Note that the apparent troughs before 24, 36, and 48 mo suggest evidence of age rounding up during data collection (where, for instance a 3.75-y-old is recorded as 4 y and hence appears smaller than in reality). In addition, an analysis of the African data sets presented in Table 4 of the Victora et al summary (1) shows that two-thirds of the data sets show some catch-up between 24 and 48 mo even in the absence of interventions (Figure 2), albeit very modest compared with the initial decline.

CELL PROLIFERATIVE POTENTIAL OF ORGAN SYSTEMS ACROSS THE LIFE SPAN

The timing of the growth of major organ systems in humans relative to the final attained size is shown in Figure 3. These

patterns of normal tissue development have been extensively studied in relation to the age-related sensitivity of organs to radiation damage (8). In relation to musculoskeletal tissues, the subject of the current discussion, growth is partitioned into 2 periods of sensitivity (<5 y and puberty) and an intervening period of relative growth quiescence. These periods are clearly shown in Figure 3.

Karlberg (9) has taken an alternative approach in the development of his infancy-childhood-puberty model of human growth in which he identifies 3 partly superimposed and additive phases: 1) a sharply decelerating infancy component representing a continuation of fetal growth; 2) a very slowly decelerating childhood component that begins in the second half of infancy and continues to maturity; and 3) a sigmoid-shaped pubertal phase that is superimposed on the continuing childhood growth. The hormonal regulators of these 3 phases differ markedly; hence, their positive modulation by nutritional intervention may also require different approaches. Regulation of the infancy phase is likely to involve numerous interacting systems, especially insulin and the insulin-like growth factors and

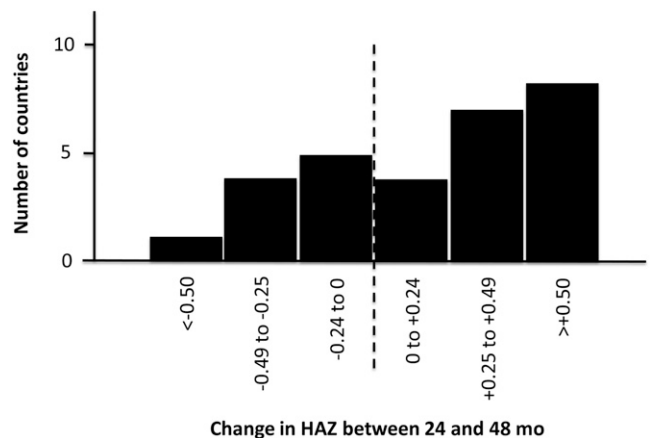


FIGURE 2. Changes in HAZs between 24 and 48 mo in 30 African countries. Calculated from data provided in Table 4 of reference 1. HAZ, height z score.

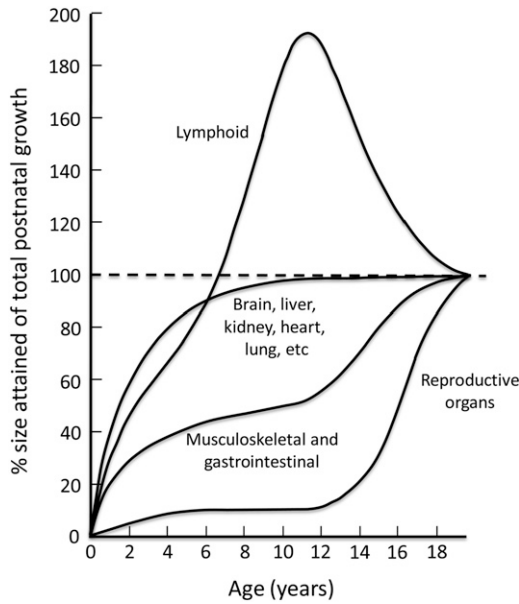


FIGURE 3. Differential timing of the growth of body systems in humans.

their competitive binding proteins. The childhood phase corresponds to the additional effect of growth hormone on these axes and in the pubertal phase growth is further augmented by sex steroids: estrogen in girls and testosterone in boys. Karlberg (9) proposes that the profound early faltering in HAZ seen in poor populations represents a developmental delay in the initiation of the childhood phase, which starts in the second 6 mo of life in well-nourished children and is much delayed in undernourished children. This interesting suggestion has not gained wide currency and merits closer scrutiny because it may point to hitherto unexplored intervention strategies.

In total, these data on the normal patterns of human development remind us that, although a high proportion of neuronal tissue is in place by 24 mo, most other tissues grow and develop after this age.

CATCH-UP IN HAZ OCCURS AFTER 24 MO IN MANY POOR POPULATIONS

Early height growth in 5 populations (Brazil, Guatemala, India, Philippines, and South Africa), each studied longitudinally and brought together in the Consortium of Health Oriented Research in Transitioning Societies (COHORTS) collaboration (10), is shown in **Figure 4**. The data confirm the rapid fall-off in HAZ between birth and 24 mo in all 5 countries, but show significant regain between 24 and 48 mo in 4 of the 5 cohorts. Both the fall-off and catch-up occur irrespective of the final height attained. India is a distinct outlier with no signs of catch-up. Data from our own studies in rural Gambia confirm the former pattern and show mean HAZ scores of -2.44 (95% CI: $-2.50, -2.39$) at 24 mo, -2.31 ($-2.36, -2.25$) at 48 mo, and -1.78 ($-1.85, 1.72$) at 72 mo (see Height Growth in Poor Rural Gambians Throughout the Life Cycle for more detail).

These examples of height catch-up in young children, even in the absence of external nutritional interventions, clearly contradict the widely held impression that a window of opportunity closes at 24 mo of age. The data in Figures 2 and 4 both emphasize that the extent of catch-up after 24 mo is highly context specific and presumably reflects the availability of foods, food-consumption patterns, the composition of diets, and the prevailing burden of infections (especially those affecting gastrointestinal function). Epigenetically mediated early life and/or intergenerational effects may also contribute to population diversity in later growth.

HEIGHT GROWTH IN POOR RURAL GAMBIANS THROUGHOUT THE LIFE CYCLE

The Medical Research Council’s field station in Keneba, The Gambia has been monitoring the anthropometric status of the poor subsistence-farming population of 3 rural villages for >6 decades. LOWESS-smoothed curves through 36,828 cross-sectional length/height measurements for males and females, expressed as HAZs against the UK 1990 reference curves, are shown in **Figure 5, A and B** (11). The similarity of the patterns when separated into data

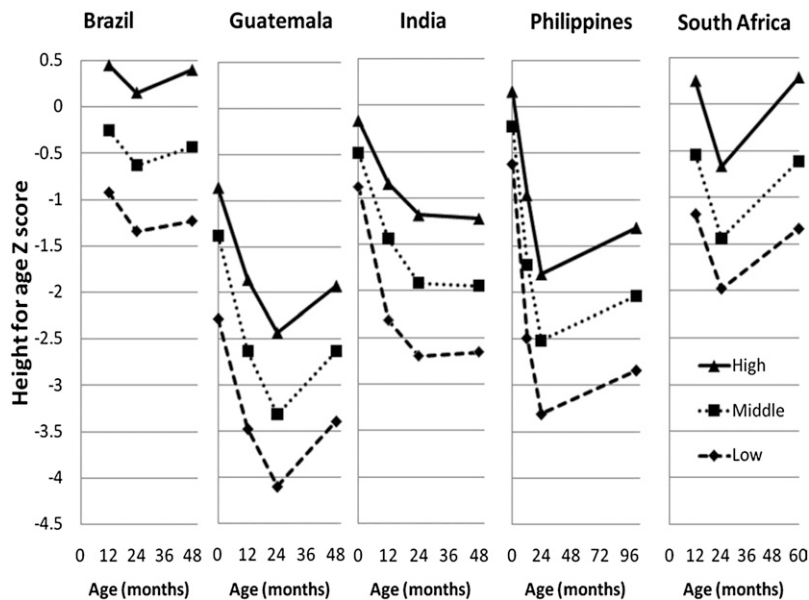


FIGURE 4. Mean height-for-age z scores and changes in height-for-age z scores for participants in the Consortium of Health Oriented Research in Transitioning Societies studies, divided by tertiles of adult height. Reproduced with permission from reference 10.

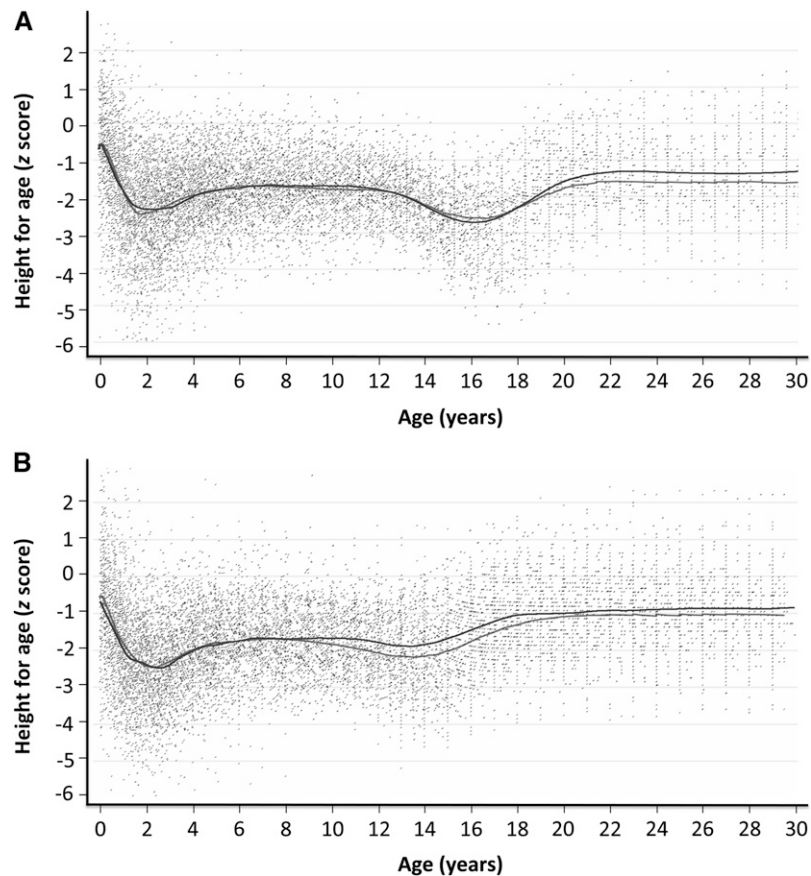


FIGURE 5. LOWESS-fitted curves applied to semilongitudinal data on growth collected between 1951 and 2006 in rural Gambia ($n = 36,828$ data points). Height-for-age z scores were calculated against the UK 1990 reference (11). Panel A = males, panel B = females. Curves drawn for data collected before and after 1970 illustrate the robustness of the growth patterns. The slightly higher lines in adulthood are the post-1970 data.

logged before and after 1970 confirms the robustness of patterns. Both sexes showed a characteristic pattern of being short at birth (~ -0.75 HAZ), falling off precipitately to 24 mo (to ~ -2.25 to -2.5 HAZ), followed by some catch-up to 5 y (to ~ -1.75 HAZ), a period of stability, followed by a further apparent drop off (which is solely an artifact arising from their later entry into puberty than the children in the UK standards), followed by an extended catch-up until a late achievement of adult stature (at ~ -1.5 HAZ in males and ~ -0.75 HAZ in females). The first phase of this adolescent catch-up is the reversal of the artifact caused by delayed initiation of puberty, but there is an additional important component represented by a prolonged growth to the age of ~ 22 – 24 y in boys and 18 – 19 y in girls. The weight-for-age curves show very similar patterns (*see* Supplemental Figure 1 under “Supplemental data” in the online issue). This maturational delay, which allows catch-up by prolonging the childhood and pubertal growth phases, was previously described in developing countries (eg, 12, 13), together with the differential timing in boys and girls (14). Studies in previously malnourished children have also shown catch-up against unaffected siblings, with some evidence that girls show a greater potential for pubertal catch-up (15). Intriguingly, there is a parallel between the catch-up growth shown after infancy and in adolescence, which suggests that both might be explained by a developmental delay in entering the next phase of growth.

In this cross-sectional analysis, the observed catch-up growth after 24 mo could arise as a result of selective mortality of the

most stunted infants. To check for this we repeated the analysis using only subjects surviving beyond 15 y and showed essentially identical values (*see* Supplemental Figure 2 under “Supplemental data” in the online issue). Note also that, in this cross-sectional analysis, there is no statistical requirement to adjust for regression to the mean, as is indicated for longitudinal assessments of catch-up (16) and as should be applied to the COHORTS longitudinal data cited above to differentiate the components of catch-up attributable to regression to the mean from true population catch-up. Our interpretation of childhood catch-up after 24 mo is that a combination of the normal postnatal maturation of the children’s immune systems and the development of a broad repertoire of adaptive responses against previously encountered pathogens reduces the frequency and severity of growth-impairing infections—a hypothesis that is supported by morbidity surveillance and clinic records.

We also studied cohorts of 80 boys and 80 girls longitudinally from 8 to 12 y (mean age 10 y; prepuberty in this setting) to 24 y (17, 18). Their height data are plotted in **Figure 6**, which again shows substantial catch-up during an extended pubertal growth phase; boys caught up from -1.25 to -0.5 HAZ and girls caught up from -1.1 to -0.2 HAZ.

The COHORTS data from 5 countries (10) also show variable levels of HAZ catch-up between midchildhood (defined as 48 mo in their analysis) and adulthood; the most malnourished populations (Guatemala, India, and Philippines) had an average

gain in HAZ of 0.72 (Table 1). Between 24 mo and adulthood, these 3 cohorts showed catch-up averaging +0.97 HAZ; among all 5 cohorts, it was notable that those most stunted at 24 mo showed the greatest height gain to adulthood. Our longitudinal Gambian data (-2.25 HAZ at 24 mo and 2.0 HAZ catch-up to adulthood) fits this general observation but shows even greater catch-up. Note that, as indicated above, a component of catch-up between successive ages can relate to regression to the mean; however, because children in COHORTS were in some cases recruited at birth, this adjustment is less critical for subsequent age intervals. Much of the analysis of COHORTS data are performed by using anthropometric changes conditional on the previous measurement to overcome these

complexities, and readers are referred to the source articles for a full description of these analyses (10, 19).

NUTRITIONAL INTERVENTIONS DURING PREGNANCY SHOW LIMITED FETAL GROWTH ENHANCEMENT

For many years we have been strong proponents of testing dietary intervention during pregnancy and have conducted several randomized controlled trials (RCTs) (20, 21) to inform the appropriate timing (eg, season or stage of pregnancy/lactation) and composition of interventions. We remain convinced of the importance of providing optimal nutrition to reproductive women, but an objective interpretation of current meta-analyses of RCTs in pregnancy provides little grounds for optimism in terms of growth enhancement. The Cochrane review of balanced protein-energy supplementation, updated to February 2010 (22), showed non-significant increases in birth weight of 49 g (95% CI: -2, 101 g) and in birth length of 0.10 cm (95% CI: -0.06, 0.26 cm), equivalent to a weight-for-age z score (WAZ) of 0.10 and 0.05 HAZ. There was, however, a significant reduction in the proportion of small-for-gestational-age infants.

A meta-analysis of 17 prenatal zinc supplementation trials showed an effect size of 0.03 (fixed effects model) or 0.07 (random-effects model), neither of which is significant (23). A meta-analysis of 49 trials of iron and folic acid similarly found no effect on birth weight or prevalence of low birth weight (24). A meta-analysis of the 12 UNIMMAP (UNICEF/WHO/UNU international multiple micronutrient preparation) multiple micronutrient RCTs in pregnancy yielded a mean increase in birth weight of 22.4 g (equivalent to 0.04 WAZ) (25).

There are likely multiple reasons for these disappointing outcomes, but they cannot be explained away on the basis of poorly conducted trials. Furthermore, if these highly controlled efficacy trials cannot show a major effect on birth size, the achievement of meaningful effects in real-life effectiveness studies would be even more challenging. The strong effect of maternal body size (height, prepregnancy weight, and attained weight in the third trimester) on intrauterine growth computed by the WHO Collaborative Study on Maternal Anthropometry and Pregnancy Outcomes (26) suggests that these variables limit how much can be achieved by intervention in pregnancy alone. Furthermore, Yajnik et al (27) have argued that nutritional interventions in mothers of small stature arising from a lifetime of undernutrition might possibly do more harm than good by inducing what he terms the “thin-fat” infant syndrome. This describes a phenotype of small infants with inappropriately large central fat stores that are associated with adverse metabolic sequelae in later life (28). Work by our group has also shown that calcium supplementation of pregnant women designed to boost breast-milk calcium supply to their infants had a paradoxical negative effect on maternal bone health (29).

COMPLEMENTARY FEEDING INTERVENTIONS DURING EARLY CHILDHOOD SHOW LIMITED GROWTH ENHANCEMENT

A systematic review of 29 efficacy and 13 effectiveness trials of complementary feeding interventions in developing countries was published by Dewey and Adu-Afarwuah (30). Provision of complementary foods achieved mean effect sizes of 0.26 (range:

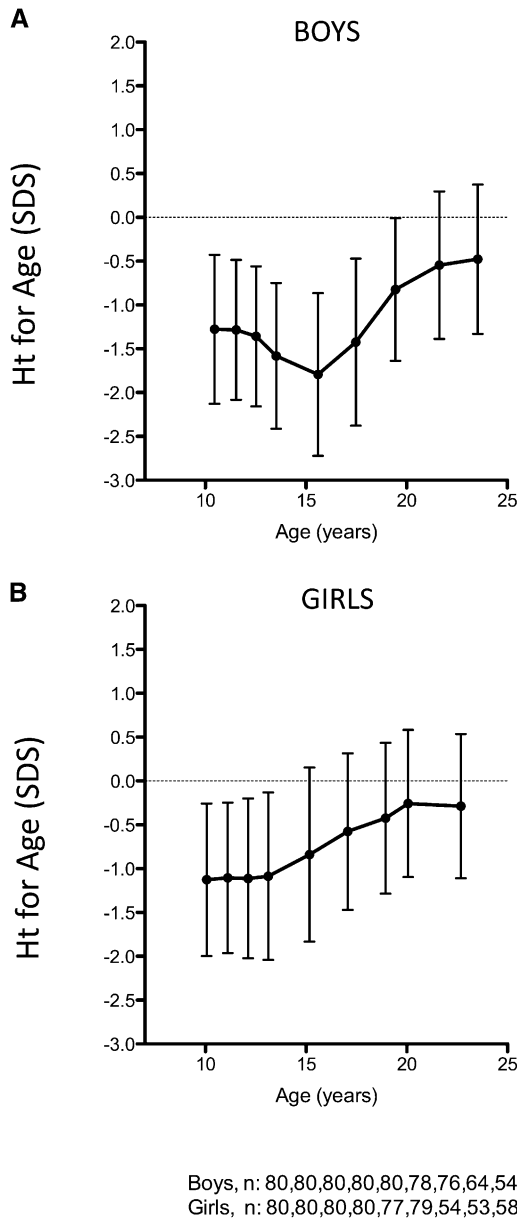


FIGURE 6. Changes in height relative to the UK 1990 reference (11) in cohorts of 80 boys and 80 girls (17, 18) measured longitudinally in rural Gambia. Loss-to-follow up rates were low, as indicated at the base of the figure. Ht, height; SDS, SD score.

TABLE 1
Changes in height-for-age z scores from birth to maturity in 5 countries from the COHORTS study¹

	Brazil	Guatemala	India	Philippines	South Africa
Height-for-age z score at time of measurement					
Birth	—	-1.47	-0.53	-0.22	—
12 mo	-0.24	-2.65	-1.54	-1.72	-0.50
24 mo	-0.61	-3.28	-1.94	-2.54	-1.37
Midchildhood	-0.43	-2.65	-1.95	-2.39	-0.56
Adult	-0.35	-1.91	-1.08	-1.85	-0.60
Change in height-for-age z score over interval					
24 mo to midchildhood	+0.17	+0.63	-0.01	+0.15	+0.71
Midchildhood to adult	+0.08	+0.74	+0.87	+0.54	-0.04

¹Midchildhood measurements were made at 48 mo (Brazil, Guatemala, and India), 60 mo (South Africa), and 102 mo (Philippines). Data from reference 10. COHORTS, Consortium of Health Oriented Research in Transitioning Societies.

-0.02 to 0.57) for weight (WAZ) and 0.28 (range: -0.04 to 0.69) for linear growth (HAZ). Provision of complementary foods and at least one additional intervention (usually education) achieved effect sizes of 0.35 (range: 0.18 to 0.66) for weight and 0.17 (range: 0 to 0.32) for linear growth. Trials aimed at increasing the energy density of the usual complementary foods had mean effect sizes of 0.35 (range: -0.13 to 1.37) for weight and 0.23 (range: -0.25 to 0.71) for linear growth. Studies with micronutrient fortification of usual weaning foods had a substantially smaller effect.

The authors rightly emphasize that the trials yielded other benefits in terms of improved micronutrient status and reduced rates of anemia, but in the context of the current discussion their analysis underscores the fact that the range of interventions before 24 mo reported to date could only make a limited contribution to reducing stunting in poor populations. Further trials with highly fortified lipid-based nutrient supplements are in progress (*see* www.ilins.org) and with combined feeding and hygiene interventions.

A likely interpretation of these disappointing results is that the heavy burden of infectious diseases, and the associated chronic environmental gastroenteropathy that affects most children in developing countries and is the major cause of the precipitous fall-off in height-for-age in infancy, simply overwhelms attempts at intervention (31). Furthermore, nutritional anthropologists question whether there may not be an adaptive component to the growth limitation that promotes survival. Later interventions, when the children's immune systems have learned to cope with the environment, might be more effective. To use a cricket metaphor—it may be better to hit with the spin than against it.

SUMMARY EFFECTS OF INTERVENTIONS IN THE CRITICAL WINDOW OF -9 TO 24 MO

Summation of the meta-analyzed effects on length growth of intervention in pregnancy (0.05 HAZ) and through improved complementary feeding (~0.25 HAZ) yields a very modest enhancement of 0.3 HAZ. This equates to only 15% of the average HAZ deficit by 24 mo in the analysis by Victora et al (1) of the data from 54 countries.

It is conceivable that an integrated life-course approach combining pre- and postnatal interventions might yield multiplicative effects. We are currently conducting such a trial in The Gambia (ISRCTN49285450). To our knowledge there have been

only 2 previous trials of this type, each of which used a cluster-randomized design. The classic INCAP (Instituto de Nutrición de Centroamérica y Panamá) study (32) randomly assigned 4 Guatemalan villages to receive *atole* (a high-protein, high-energy supplement) or *fresco* (a no-protein, low-energy supplement) to be consumed by pregnant mothers and their offspring. Secondary analyses of this study, which also included supplementation in older children, have shown many health benefits in adults and important intergenerational effects (33, 34). A similar design in 29 villages in South India also showed modest increases in height at ages 13–18 y and improvements in other health indicators of metabolic and vascular health (35).

THE CRITICAL IMPORTANCE OF PRECONCEPTIONAL NUTRITIONAL STATUS ON PREGNANCY OUTCOMES

The effect on the incidence of neural tube defects of maternal folate status at the time of early embryogenesis (36) provides a powerful reminder of the importance of the preconceptional nutritional status of a mother. Physical status is also important. In a meta-analysis of data from 20 countries, maternal height, prepregnancy weight, and attained weight at 9 mo of gestation (lowest compared with highest quartiles) predicted both low birth weight (combined OR: 2.8) and intrauterine growth restriction (OR: 3.0) (26). Our own analysis from rural Gambia showed a highly significant 4% decrease in the odds of an infant being small-for-gestational age per 1-cm increase in maternal height (37). Pelvic size also correlates with maternal height, and taller mothers have fewer adverse obstetric outcomes.

ADOLESCENCE: AN ADDITIONAL CRITICAL WINDOW FOR NUTRITIONAL INTERVENTION?

We showed that height catch-up, of a magnitude much greater than that which has been achieved by external nutritional interventions within the -9 to 24 mo window, frequently occurs between 24 mo and adulthood, even in the absence of nutritional supplementation. Interventional studies in markedly stunted affluent children (eg, gluten exclusion in patients with celiac disease and growth hormone replacement in congenitally deficient patients) have shown a remarkable potential for height restitution throughout childhood (eg, 38, 39). Similarly, studies of stunted children adopted into affluent settings have also shown height catch-up, although the evidence indicates that early adoption predicts better gains (40).

The impressive centile crossing in HAZ (and WAZ) during adolescence shown by rural Gambian girls (Figure 5B and Figure 6) emphasizes the growth plasticity during these years and begs the question of whether growth could be further enhanced with judicious interventions aimed at maximizing a young mother's fitness to reproduce. A literature search, surprisingly, identified a handful of single-nutrient interventions in adolescence in developing countries but no comprehensive supplementation studies. We suggest that this represents an important omission. Golden (41) previously made a similar point and emphasized that full adult height potential might be achieved with sufficiently robust supplementation applied over a sufficient duration. The possibility remains, however, that intergenerational epigenetic limitations have been imprinted that would take several generations to erase (42).

Any such studies would need to be most carefully considered with respect to timing and composition of the supplementation and should be accompanied by interventions to minimize teenage pregnancies. One Swedish study of late-adopted Asian children cautions that accelerated growth might shorten the growth period by hastening closure of the growth plates and, therefore, may paradoxically lead to shorter adult stature (43). The adoptee literature would form an important basis for designing testable intervention strategies. Our own recently published data suggest that there may be complex, potentially sex-differential, feed-forward influences of nutritional interventions in childhood on the subsequent timing of peak height velocity and growth cessation that require further study (18). Examination of the sensitivity to dietary manipulation of both the growth hormone-stimulated childhood growth component and the sex hormone-stimulated pubertal component, and the interactions between them, would be important.

Given the current background of the very limited efficacy of nutritional interventions in the -9 to 24 mo window, it is important that an excessive focus on the first 1000 d does not inhibit efforts to examine other life stages that may be more sensitive to intervention. Interventions beyond 24 mo that prove successful in enhancing adult stature (especially in girls) may offer additional opportunities to improve nutritional status and would likely foster advantages throughout the mothers' entire reproductive life and benefit future generations.

We thank generations of mothers, infants, and children in the villages of Keneba, Manduar, and Kantong Kunda for their dedication to medical research. The Bakary Dibba Study, which provided data for Figure 6, was initiated by our deceased friend and colleague Bakary Dibba.

The authors' responsibilities were as follows—AMP: conceived and coordinated the analyses, wrote the manuscript, and had primary responsibility for the final content; KAW, GRG, LMJ, and AP: ran the BDS longitudinal study and performed the longitudinal growth analyses; AP: conceived the BDS study; AJF and SEM: oversaw all aspects of the anthropometric data collection at MRC Keneba; and AJF: conducted the cross-sectional analyses. All authors contributed to the data interpretation and approved the final manuscript. None of the authors reported a conflict of interest.

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