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Recent Advances in Growth Research: Nutritional, Molecular and Endocrine Perspectives

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Contents

ix  Preface
xi  Foreword
xv  Contributors

Drivers of Growth

1 Early Influences of Nutrition on Fetal Growth
   Makrides, M.; Anderson, A.; Gibson, R.A. (Australia)

11 Early Influences of Nutrition on Postnatal Growth
   Koletzko, B.; Beyer, J.; Brands, B.; Demmelmaier, H.; Grote, V.; Haile, G. (Germany);
   Gruszfeld, D. (Poland); Rzehak, P. (Germany); Socha, P. (Poland); Weber, M.
   (Germany); for The European Childhood Obesity Trial Study Group

29 Genome-Wide Association Studies of Human Growth Traits
   Weedon, M.N. (UK)

39 Discussion on Nutrition and Genetics
   Clark, A.J.L. (UK)

43 IGF-I in Human Growth: Lessons from Defects in the GH-IGF-I Axis
   Hwa, V.; Fang, P.; Derr, M.A.; Fiegerlova, E.; Rosenfeld, R.G. (USA)

57 Non-Imprinted Epigenetics in Fetal and Postnatal Development and
   Growth
   Godfrey, K.M.; Lillycrop, K.A.; Burdge, G.C. (UK); Gluckman, P.D. (New Zealand);
   Hanson, M.A. (UK)

65 Epigenetic Anomalies in Childhood Growth Disorders
   Netchine, I.; Rossignol, S.; Azzi, S.; Le Bouc, Y. (France)

75 Early Growth and Development of Later Life Metabolic Disorders
   Foo, J.-P.; Mantzoros, C. (USA)

85 Summary on Drivers of Growth
   Gluckman, P.D. (New Zealand)
Secular Trends in Growth

89 Human Growth: Evolutionary and Life History Perspectives
Gluckman, P.D. (New Zealand/Singapore); Beedle, A.S. (New Zealand); Hanson, M.A. (UK); Low, F.M. (New Zealand)

103 Secular Trends in Birthweight
Oken, E. (USA)

115 Secular Changes in Childhood, Adolescent and Adult Stature
Bogin, B. (UK)

127 Discussion on Human Biology in Motion
Ellison, P.T. (USA)

131 Economic Drivers and Consequences of Stunting
Alderman, H. (USA)

143 Discussion on Economic Drivers and Consequences of Stunting
Adair, L.S. (USA)

147 Epidemiologic Transitions: Migration and Development of Obesity and Cardiometabolic Disease in the Developing World
Forrester, T. (Jamaica)

157 Discussion on Migration and Development of Obesity and Cardiometabolic Disease in the Developing World
Adair, L.S. (USA)

What Is Healthy Growth?

161 State of the Art of Growth Standards
Weaver, L.T. (UK)

171 Healthy Infant Growth: What Are the Trade-Offs in the Developed World?
Belfort, M.B.; Gillman, M.W. (USA)

185 Discussion on Growth Standards and Trade-Offs in Healthy Infant Growth
Law, C. (UK)

191 Relationship between Childhood Growth and Later Outcomes
Ferraro, A.A.; Bechere Fernandes, M.T. (Brazil)

199 Public Policy Implications of Promoting Growth
Wise, P.H. (USA)

207 Pharmacological Interventions for Short Stature: Pros and Cons
Rosenfeld, R.G. (USA)
Discussion on Childhood Growth and Later Outcomes, Policy Implications and Treatment of Short Stature
Stein, A.D. (USA)

Concluding Remarks
Subject Index

For more information on related publications, please consult the NNI website: www.nestlenutrition-institute.org
Preface

Among all biological phenomena, the growth of organisms is perhaps the most complex process. In mammals, this must encompass intrauterine growth as well as the distinct growth trajectories of infancy, childhood and adolescence. Each of these phases has evolved in a manner suited to the distinct metabolic, survival and reproductive demands of the particular species. And, as captured in the title of the 71st Nestlé Nutrition Institute Workshop, each of these phases is characterized by very specific nutritional, molecular and endocrine perspectives, which, under ideal conditions, allow the organism to achieve its genetically programmed growth patterns. The Workshop thus represents an effort to address these complexities, individually and collectively, with the goal of discussing these aspects historically (i.e. within an evolutionary framework), physiologically (i.e. from a molecular and biochemical perspective) and socially (i.e. how do we meet the requirements for normal growth within an overpopulated and resource-deprived world).

Session 1 (Drivers of Growth) is directed at an understanding of the genetic, epigenetic, molecular and nutritional determinants of intrauterine and postnatal growth. Among the questions addressed are the influence of nutrition on growth in utero and during infancy, lessons learned from genome-wide association studies of normal growth and candidate gene approaches to abnormal growth, and the impact of both imprinted and nonimprinted epigenetics on fetal and postnatal growth.

Session 2 (Secular Trends in Growth): While evolution over the thousands or millions of years of any species has resulted in significant changes in body size, it is clear that there have been secular changes in growth over much shorter time periods, as brief indeed as a century. One of the most remarkable phenomena in human growth has been the increase in height and the advancement of puberty in Third World countries, presumably reflecting improved nutrition and health. It is thus important to look at changes in body size in utero, during infancy and childhood, and during adolescence, to best understand the individual and collective impact of improved health upon human growth. While one may look at improved growth as a sign of organismal health, there are also potentially
unfavorable consequences of enhanced nutrition and growth, including early onset of puberty, development of obesity, and increases in metabolic and cardiovascular disease. The challenge thus involves maximizing the potential for normal growth without increasing the risk of associated disorders.

Session 3 (What Is Healthy Growth?): In light of the influence of nutritional, molecular and endocrine influences upon growth, and given the clear-cut secular changes in both linear growth and body mass, the question arises as to what factors define healthy growth. Standard growth curves derived from calculating means and standard deviations of various auxologic parameters are fine from a statistical perspective, but do not in and of themselves determine optimal growth. This point is especially important in developing countries, which have seen rapid changes in body size, often accompanied by altered patterns of metabolic and cardiovascular disease. Although this association is clear, the precise nature of causality remains uncertain. Critical issues include how to define optimal intrauterine and postnatal growth and what are the roles of pharmacological intervention and public policy.

These are several of the critical issues addressed in the 71st Nestlé Nutrition Institute Workshop held in Vienna, Austria, on October 23–26, 2011. It is the hope of the editors that the papers included in this volume will shed some needed light on these important matters.

Matthew W. Gillman
Peter D. Gluckman
Ron G. Rosenfeld
Foreword

The 71st Nestlé Nutrition Institute Workshop Pediatric Program ‘Recent Advances in Growth Research: Nutritional, Molecular and Endocrine Perspectives’ took place in October 2011 in Vienna (Austria).

Growth and development during the fetal and postnatal periods as well as during the first 2 years of life are important for short- and long-term health. There are many growth drivers during this phase of life, among them nutrition, genetic and epigenetic factors, and hormonal regulation.

Thus, the scope of the workshop was to focus on the latest scientific findings in growth research.

The Nestlé Nutrition Institute Workshop brought to discussion the questions which have been circulating in the scientific community during the last decade: how feeding in early life influences long-term growth and development, and the risks which are related to inadequate nutrition such as obesity and malnutrition. In addition, the workshop program covered the potential health economic impact of stunting.

The 3 days of intense scientific discussions have crystallized again the importance of understanding the value of breastfeeding and, in case of non-availability of breast milk, how appropriate nutrition can prevent nutritional disorders and long-term metabolic consequences.

We wish to warmly thank the three chairpersons of this workshop – world-renowned experts in the area of child growth and development – Prof. Matthew Gillman, Prof. Sir Peter Gluckman and Prof. Ron Rosenfeld for establishing an excellent scientific workshop program.

We are also indebted to the renowned speakers and discussants who have furthered the debate and understanding of this important topic through their presentations and participation. We thank the many experts who came from across the globe to review and discuss the importance of child growth and development.
Finally, we wish to thank and congratulate Dr. Mike Poßner and his team from Nestlé Nutrition Institute – Europe for their excellent logistical support that allowed us all to enjoy the scientific program and the vital spirit of Vienna.

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Early Influences of Nutrition on Fetal Growth

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Abstract

During pregnancy, the metabolic requirements of the mother are increased; however, the relationship between maternal intake of key nutrients and optimal fetal growth is not always clear. In this chapter, we have reviewed randomized controlled trials of nutritional interventions during pregnancy, with a particular focus on birthweight and infants who are small for gestational age (SGA). Of the trials that have investigated changing macronutrient and energy intakes during pregnancy, supplements in which <25% of the energy is provided by protein yielded the most promising results, producing a 31–32% reduction in the risk of SGA infants and an increase in birthweight (38–60 g) compared with control. Single-nutrient intervention trials using n-3 long-chain polyunsaturated fatty acid (LCPUFA) supplements demonstrated small increases in birthweight (=50 g) and birth length (=0.5 cm), which may be explained by small increases in gestation length (approximately 2.5 days). n-3 LCPUFA supplementation in pregnancy did not however decrease the proportion of SGA infants. Multiple-micronutrient supplementation trials in developing countries have resulted in increased mean birthweight (22–44 g) and reduced the risk SGA by 9–15%. Further nutritional intervention studies which are rigorously designed and implemented are needed particularly to delineate differential effects in developed and developing countries.

Infants with restricted intrauterine growth are more likely to have poor cognitive development during childhood, and later in life are also at increased risk of cardiovascular, pulmonary and renal disease. Prevention of low birthweight
and growth restriction in utero is therefore an important target with the potential to improve the long-term outcome of children. It is therefore not surprising that many studies have focused their attention on improving the quality of the maternal diet during pregnancy in order to promote the growth of the fetus. However, it is evident that the relationship between maternal nutrition and fetal growth is not a simple one. Apart from maternal nutrition, there are many factors that influence the size of the infant at birth including genetic potential, the size of the mother, the success of placentation and delivery of nutrients to the fetus, pregnancy and metabolic adaptation to protect the fetus, other environmental stresses such as cigarette smoking and alcohol. In fact, some of these factors may play a greater role in influencing the size of the baby at birth, and it may be for this reason that it has been challenging to decipher the true effect of maternal diet during pregnancy on fetal growth. The scope of this chapter is to review the effects of maternal dietary intakes on the growth of the fetus with a particular focus on birthweight and the proportion of infants born who are growth restricted or small for gestational age (SGA). As we are interested in deciphering cause and effect relationships between maternal dietary intakes during pregnancy and birth size, the review is limited to randomized controlled trials that have been designed to assess the effects of specific nutritional interventions during pregnancy and have included birth size as an outcome.

The published intervention trials can be grouped into four categories: (1) macronutrient interventions that have increased energy, (2) macronutrient interventions that have decreased energy, (3) single-nutrient interventions that have not altered energy intake and (4) multiple nutrient, generally micronutrient, interventions that also have not altered energy intake.

**Macronutrient Interventions That Have Varied Energy**

Observational studies have consistently reported that gestational energy intake is strongly and positively associated with fetal growth. The most commonly cited example is the Dutch Famine Study that found a clear association between the forced restriction of energy intake in the third trimester and reduced fetal growth [1]. It therefore logically follows that macronutrient intervention to increase energy intake during pregnancy will increase fetal growth, while macronutrient interventions to decrease energy will decrease fetal growth.

**Macronutrient Interventions That Increase Energy**

The majority of trials that have investigated the effect of dietary macronutrient manipulation have focused on the protein energy balance and these are often split into supplements which provide <25% of the energy content as protein (protein energy ratio of <0.25) and supplements which provide >25% of the energy content.
as protein (protein energy ratio >0.25) [2]. To put this into context, many foods contain <25% energy as protein including whole milk and nuts, while lean meat and cheese are among the relatively few foods to contain >25% energy as protein.

**Energy Supplementation in Which Protein Contributes <25% Energy**

Two systematic reviews and meta-analyses of intervention studies have investigated the effects of supplements with a protein energy ratio of <0.25 during pregnancy on birth outcomes [2, 3]. The included studies tested various supplements, and where documented the protein content ranged from 6 to 40 g per day and provided 322–1,017 kcal of extra energy per day. The supplements were either beverages or solid foods, and were generally administered after 20 weeks' gestation. Blackwell et al. [4] started supplementation after a prior birth and continued during the index pregnancy, while Elwood et al. [5] began supplementation at the time of first reporting the pregnancy. These intervention trials were generally not well controlled as the vitamin and mineral levels in the control supplements did not match those in the energy supplement, but in many cases the control intervention was no treatment. Additionally, concealment of randomization was not always clearly reported, and because of the nature of the interventions blinding of participants was not always possible. Blinding of the assessors was also not always reported.

Despite these limitations, both meta-analyses revealed that supplements with a protein energy ratio of <0.25 during pregnancy resulted in a 31–32% reduction in the risk of SGA infants (relative risk, RR, 0.68–0.69; 95% confidence interval, CI: 0.56–0.84/0.85) [2, 3]. Participants in 5 of the 6 trials were undernourished. When the trial relating to adequately nourished women was excluded from the analysis, the RR became 0.66 (95% CI: 0.53–0.82) [3].

Pooled results in both systematic reviews, from 11–12 trials, showed that supplementation with a protein energy ratio of <0.25 also resulted in an increase in birthweight of approximately 38–60 g. Discrepancies in the magnitude of the increase reflect differences in inclusion criteria and weighting of the trials in the meta-analyses. Both reviews demonstrated a greater effect of supplementation on mean birthweight in undernourished women; however, the magnitude and significance of the increase (approximately 50–75 g) was again dependent on the criteria established in the reviews. No significant differences were found in birth length, head circumference or gestational age (GA) [2].

A 37–38% reduction in the risk of neonatal mortality, based on results of 3–4 trials, was also detected in both reviews (RR, 0.62–0.63; 95% CI: 0.37–1.05/1.06) [2, 3]; however, the results did not reach significance in either review.

**Energy Supplementation in Which Protein Contributes >25% Energy**

Few studies have addressed the effect of protein energy supplements that provide >25% energy as protein during pregnancy on birth size. Such supplements are challenging to construct and are unlikely to be palatable. However, two trials
have intervened with high protein supplements based on beverages containing dried skimmed milk. Supplementation was associated with a nonsignificant reduction in birthweight (mean difference, MD, –58 g; 95% CI: –146 to 29 g) [2]. One of these trials [6] also reported a nonsignificant increased risk of neonatal death, mainly in pregnancies where infants were born prior to 37 weeks’ GA with the protein supplement providing >25% of energy.

**Macronutrient Interventions That Decrease Energy**

The increased prevalence of obesity in many industrialized countries naturally implies that many more women who are overweight or obese are entering pregnancy. These women are at increased risk of pregnancy complications and poor pregnancy outcomes. With this rationale, several trials with small numbers of women (20–90 per group) have investigated the effect of energy restriction during pregnancy on birth size. The target energy intakes in the intervention groups were variable, and some were relatively severe and required women to reduce their energy intakes by at least 1,000 kcal per day. Although the interventions were uniformly successful at reducing weekly gestational weight gain, the meta-analysis indicated significant heterogeneity which could have been related to the differing interventions and/or the differing population groups [2]. The effect of energy restriction during pregnancy on birthweight in overweight women also exhibited significant heterogeneity with the three included trials showing either no effect of intervention, a large negative effect (MD –450 g; 95% CI: –625 to –275 g) or a nonsignificant negative effect (MD –138 g; 95% CI: –450 to 174 g).

On the basis of the trials reviewed so far, supplements with a protein energy ratio <0.25 during pregnancy may be worthy of consideration as a public health intervention to reduce the risk of SGA infants. The positive effects of supplements with a protein energy ratio <0.25 were more pronounced in populations that were not adequately nourished, but this finding should be interpreted with some caution as the trials did not use standardized maternal body mass index cutoffs to assess undernutrition [3]. Further carefully controlled RCTs would be beneficial, in both developed and developing countries, to ascertain with more certainty the optimum amounts of supplementation and best timing of the intervention. Conversely, the limited data available from RCTs indicate that energy restriction during pregnancy appears to have negative consequences on fetal growth even for women who are overweight or obese. A recent retrospective cohort study [7] has investigated associations of gestational weight loss (GWL) and birth outcomes. Although GWL was associated with a decreased risk of pregnancy complications in obese and overweight women, it was also associated with increased risks of SGA infants (OR, 1.68; 95% CI: 1.37–2.06) in all maternal BMI groups, except for underweight women. Large-scale RCTs currently in progress will be important to determine the metabolic and health consequences for both mother and child.
**Nutrient Interventions That Do Not Vary Energy**

**Single-Nutrient Interventions**

As the deficiency of specific nutrients such as zinc is known to be associated with growth failure in early life, it is interesting to consider whether supplementation of specific nutrients during pregnancy has a role in fetal growth. However, intervention trials involving single-nutrient interventions, including iron, zinc or calcium, have not yielded consistent or promising results that would indicate that maternal intervention with these single nutrients would change fetal growth [8–10].

Of specific interest are the n-3 long-chain polyunsaturated fatty acids (LCPUFA). n-3 LCPUFA are actively incorporated into all cellular membranes, and are postulated to have an important role in delaying parturition. It is hypothesized that n-3 LCPUFA can delay initiation of labor and cervical ripening by inhibiting the production of prostaglandins F₂α and E₂. These mechanisms together with observational studies suggesting that women consuming high n-3 LCPUFA from marine sources have longer gestations and babies with higher birthweights than women who consume low levels of n-3 LCPUFA led to a number of intervention trials that have been summarized in three separate systematic reviews [11–13]. The meta-analyses showed remarkably consistent results despite the fact that these reviews had differing inclusion criteria based on women’s risk of adverse pregnancy outcomes. In brief, supplementation with marine oil (usually 3 g n-3 LCPUFA) in the second half of pregnancy resulted in higher mean birthweights (approximately 50 g) and higher mean birth lengths (0.48 cm) in the marine oil groups compared with control [11–13]. However, it is important to note that there was also a modest increase in the length of gestation (approximately 2.5 days) with marine oil treatment. The small increases in birthweight and length with n-3 LCPUFA treatment could probably be explained by the small increase in length of gestation. Furthermore, there were no overall differences between the groups in the proportion of SGA babies [11]. It is therefore entirely feasible to suggest that the observed increases in birthweight and birth length with n-3 LCPUFA supplementation are a function of the increased duration of gestation.

Two recent large intervention trials have investigated the effect of two different doses of n-3 LCPUFA, namely, an Australian study in which 2,399 women were allocated 1 g/day of n-3 LCPUFA mostly as docosahexaenoic acid (DHA; 800 mg/day) or control [14] and a trial conducted in Mexico in which 1,094 women were allocated to 400 mg DHA/day or control [15]. In both trials, supplementation was from mid-gestation until birth. Consistent with the systematic reviews, the Australian study [14] reported a small increase in the median duration of gestation, a significant reduction in early preterm birth <34 weeks (RR, 0.49; 95% CI: 0.25–0.94), no clear effect on preterm birth <37 weeks (RR, 0.77; 95% CI: 0.56–1.05) and increased obstetric intervention ( inductions and elective
caesarean sections) because of post-term dates (RR, 1.28; 95% CI: 1.06–1.54). This increase in pregnancy duration was reflected in higher mean birthweight with n-3 LCPUFA treatment (MD 68 g; 95% CI: 23–114 g) and a reduction in the frequency of birthweight less than 2,500 g (RR, 0.65; 95% CI 0.44–0.96). However, the birthweight z score did not differ between groups, indicating that there was no difference with correction for GA and sex using z scores [14]. Conversely, Ramakrishnan et al. [15] reported that mean GA at birth did not differ between groups (39.1 weeks, standard deviation, SD, 1.7 weeks vs. 39.0, SD 1.9 weeks) nor did birthweight (3.20 kg, SD 0.47, vs. 3.21 kg, SD 0.45), birth length or birth head circumference. However, the babies of women experiencing their first pregnancy were heavier (MD 99 g; 95% CI: 5–193) and had larger head circumferences (MD 0.5 cm; 95% CI: 0.1–0.9) at birth compared with controls [15]. There were no differences in birth size for the offspring of multigravida women [15]. The disparity between the two studies may relate to the different doses of n-3 LCPUFA tested as most trials included in the systematic reviews assessed the effect of 3 g n-3 LCPUFA per day, and it may be that at least 1 g n-3 LCPUFA per day is required to see the effect on pregnancy duration. Clearly, further work is required to clearly delineate whether there is any effect of n-3 LCPUFA supplementation on fetal growth independent of pregnancy duration.

Multiple Nutrient Interventions

The concept of multiple-micronutrient supplementation for undernourished women is particularly noteworthy because in most situations of undernutrition there is insufficiency of many micronutrients, and it is in fact quite rare to have single-nutrient deficiencies. Several systematic reviews of multiple-micronutrient interventions have been conducted recently [16–18]. Many, but not all, of the trials reviewed, used a United Nations International Multiple Micronutrient Preparation supplement and most were conducted in developing countries/rural areas. Overall, multiple-micronutrient supplementation, compared with iron-folate, resulted in increased mean birthweight by 22–44 g, reduced prevalence of low birthweight by 11–14% and reduced risk of SGA by 9–15%. One review also reported an increase in the prevalence of large for gestational age births (OR 1.13; 95% CI: 1.00–1.28) and an overall upward shift in birthweight distribution [16]. There was no significant impact on duration of gestation [16], the risk of preterm birth [16], neonatal mortality [17] or perinatal mortality [18]; however, there is considerable heterogeneity in the mortality results. Maternal education, GA at commencement of supplementation and home births were thought to contribute to the heterogeneity [17, 18]. The effects of the supplements on birthweight observed by Fall et al. [16] were also reported to be greater in women with higher BMI, suggesting that perhaps micronutrients do not have a positive influence during pregnancy if there is an ‘overriding’ maternal energy deficiency [16]. However, in a recent study in rural China, the beneficial effects of multiple-micronutrient supplementation...
on birth parameters were not seen in women from the wealthiest households [19] who would be expected to have a more adequate diet, less micronutrient deficiencies and greater access to healthcare information/services during pregnancy [19].

Few trials appear to have been conducted in developed countries. Hininger et al. [20] have investigated the effects of an iron-free multiple-micronutrient supplement on a small sample of women (n = 100) in urban France. Only 65% of women remained at the end of the study, but the supplement, compared to placebo, increased birthweight by around 10% and reduced the proportion of newborns with weights <2,700 g. Brough et al. [21] also conducted a study on a socially deprived group of women in London, UK. While only 39% of women completed this study, analysis showed there were no significant differences in mean birthweight, GA at birth, or risk of SGA between placebo and supplemented groups. However, when only compliant mothers were included in the analysis, it appeared that there may have been a role of the supplements in reducing SGA [21].

Conclusions

Collectively, the available data indicate that the protein energy ratio in the maternal diet during pregnancy is important for fetal growth. Excessive energy restriction during pregnancy is likely to limit fetal growth, while energy supplements with <25% of the energy as protein appear to increase fetal growth resulting in fewer babies born SGA. Additionally, supplements with a protein energy ratio of <0.25 seem most effective in women who are undernourished. Energy supplementation with excessive protein (>25% of energy) during pregnancy does not appear to have a clear effect on fetal growth, although the data are limited. The effect sizes observed in trials of energy supplementation of <25% energy as protein appear modest (38–60 g), accounting for 1–2% of total birthweight. However, when one considers that cigarette smoking during pregnancy reduces birthweight by 140–250 g (4–8% of total birthweight), the potential importance of nutritional intervention can be put into context. Interestingly, single-nutrient interventions in isolation probably have limited effectiveness in altering fetal growth even in women who are not well nourished. Conversely, multiple-micronutrient supplementation in undernourished women could help to support fetal growth probably because women who are undernourished are insufficient in more than one nutrient. What is not clear and has not been well investigated is the relative effect of energy supplementation with a protein energy ratio of <0.25 versus multiple-micronutrient supplementation especially since the studies of protein energy ratio also inevitably included a range of micronutrients, the concentration of which was often not controlled. Further studies, which are rigorously designed and implemented, are needed to optimize the dietary prescription for pregnant women.
References


Early Influences of Nutrition on Postnatal Growth

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Abstract

Health and nutrition modulate postnatal growth. The availability of amino acids and energy, and insulin and insulin-like growth factor-I (IGF-I) regulates early growth through the mTOR pathway. Amino acids and glucose also stimulate the secretion of IGF-I and insulin. Postnatal growth induces lasting, programming effects on later body size and adiposity in animals and in human observational studies. Rapid weight gain in infancy and the first 2 years was shown to predict increased obesity risk in childhood and adulthood. Breastfeeding leads to lesser high weight gain in infancy and reduces obesity risk in later life by about 20\%, presumably partly due to the lower protein supply with human milk than conventional infant formula. In a large randomized clinical trial, we tested the hypothesis that reduced infant formula protein contents lower insulin-releasing amino acid concentrations and thereby decrease circulating insulin and IGF-I levels, resulting in lesser early weight gain and reduced later obesity risk (the ‘Early Protein Hypothesis’). The results demonstrate that lowered protein in infant formula induces similar – but not equal – metabolic and endocrine responses and normalizes weight and BMI relative to breastfed controls at the age of 2 years. The results available should lead to enhanced efforts to actively promote, protect and support breastfeeding. For infants that are not breastfed or not fully breastfed, the use of infant formulas with lower protein contents but high protein quality appears preferable. Cows’ milk as a drink provides high protein intake and should be avoided in infancy.

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Growth and development are key characteristics of childhood and sensitive markers of health status and adequate nutrition. Pediatricians regularly monitor the growth patterns of children as part of standard routine care, usually by plotting repeated growth measures over time on percentile reference curves to derive longitudinal growth patterns. Traditionally, this approach served primarily to early detect growth faltering as a marker of the presence of infectious and other diseases, or of inadequate nutrition, which show particularly rapid adverse effects on growth in infancy and early childhood [1]. More recently, however, the impact of excessive growth on child health has been receiving increasing attention [2–4].

In 1989, Karlberg [5] described the Infancy-Childhood-Puberty Growth Model (ICP model) of growth, and proposed the key drivers of growth to be age dependent. Karlberg concluded that pubertal growth is primarily driven by sex hormones, whereas prepubertal growth is regulated primarily by human growth hormone (hGH) acting through the release of insulin-like growth factor-I (IGF-I). In addition, dietary factors and especially the intakes of energy and protein are very important regulators of serum IGF-I concentrations and its biological activity, especially during the first months of infancy [6]. Amino acids were also reported to be more potent stimulators of IGF-I release than glucose [7]. For example, studies in 4-week-old rats showed that feeding a diet with 15 instead of 5% protein for only one week increased serum IGF-I more than 4-fold [8]. With increasing age of the child, there appears to be a gradual transition to a more important role of hGH in the regulation of IGF-I, along with increasing concentrations of growth hormone-binding proteins that are considered to reflect hGH receptor numbers [9, 10]. Nutrition also markedly influences insulin secretion which has key regulatory roles for anabolic pathways as well as tissue and lipid deposition during early growth [11, 12]. Glucose concentration is a key driver of insulin secretion, but the glucose-induced insulin secretion was shown to be markedly attenuated by a low protein supply [13]. Amino acids such as leucine also enhance insulin secretion via both acute effects, such as activated glutamate dehydrogenase activity, and chronic effects such as gene transcription and regulation of β-cell metabolism [14].

One pathway though which nutrients as well as the growth factors insulin and IGF-I can effectively modulate growth and metabolism is the mammalian target of rapamycin (mTOR), a highly conserved Ser/Thr kinase present in two structurally and functionally distinct complexes [15]. The mTORcomplex 1 (mTORC1) contains mTOR, mLST8, and raptor, whereas mTORC2 is composed of mTOR, mLST8, rictor, mSin1, and PRR5. The growth factors insulin and IGF-I stimulate mTORC2 via an unknown pathway, and mTORC1 via PI3K and Akt inducing the mTORC1 activator Rheb [15]. Amino acids enhance ATP loading of RAG proteins and RAG-GTPases, which interact with Rheb and activate mTORC1 [15]. Of importance, full activation of mTORC1 is only achieved through the synergistic action of both growth factors and amino acids, while a low energy supply downregulates mTORC1 [15]. Thus, this pathway represents an elaborate sensor
system by which nutritional supply regulates metabolism and growth. The enormous power of this system is demonstrated, for example, in mice with knockout of raptor in adipose tissue, which leads to disruption of mTORC1. These mice are lean and resistant to diet-induced obesity, and they have improved metabolic characteristics such as better glucose tolerance and insulin sensitivity, as well as resistance to diet-induced hypercholesterolemia [16]. These observations lead us to the conclusion that regulation of mTORC1 signaling by amino acids controls whole-body energy metabolism, bodyweight and body composition. Therefore, the current knowledge on the physiological mechanisms regulating metabolism, growth and related outcomes relevant for health indicate the large potential that improved nutritional practice during early life can have on long-term disease prevention and well-being, a concept widely known as early nutritional programming of life-long health [17–23]. Results of a recent randomized intervention trial in human infants demonstrate the powerful effects of modifying protein supply on metabolic and endocrine response as well as growth [24].

Postnatal Diet, Growth Patterns, and the Later Risk of Obesity and Related Non-Communicable Diseases

In early systematic studies performed already in the 1960s, McCance and Widdowson [25] demonstrated programming effects of food restriction for 3 weeks in the early life of animals which led to permanent reduction of bodyweight up to adulthood, whereas no such permanent effects were induced when the same degree of food restriction was induced at a later age. In humans, such postnatal programming effects on later body size have also been reported [26]. Both high birthweight and high weight gain in the first 2 years of life are associated with increased risk for later obesity, as reviewed in Koletzko et al. [27]. For example, we found early growth patterns predictive of overweight risk at school age in a study on 4,235 German children aged 5–6 years that were participating in the obligatory school entry health examination in Bavaria, Germany. Data on early gains of weight, length, body mass index (BMI) and Ponderal Index were derived from the measurements taken during the preventive health care checks offered to all children at birth, 6, 12 and 24 months [28]. Overweight at school entry was assessed according to gender- and age-specific BMI cutoff points. Among all the anthropometric measures and time intervals assessed, weight gain from birth to age 2 years was the best predictor of overweight at school age. Similarly, many studies in other populations also found early rapid weight gain associated with an increased risk of later obesity. Several recent systematic reviews on observational studies concluded that rapid weight gain in infancy and the first 2 years of life is a significant risk indicator for later adiposity [29–32].

Figure 1 shows the increased odds of later obesity during different age categories from childhood to adulthood predicted by early rapid weight gain, defined as
an increase in weight-for-age standard deviation score (SDS) >0.67 SD [29, 33]. In addition to an increased obesity risk, high early weight gain in the first 1–2 years of life is associated with a variety of other later adverse health outcomes [34–36] such as increased risk of high blood pressure [37], increased body fat deposition [28, 38, 39], less favorable lipoprotein profiles [40], diabetes [41] and asthma [42–44].

**Protective Effects of Breastfeeding on Obesity Risk in Later Life**

Populations of breastfed infants grow somewhat differently from formula-fed populations. In poor populations challenged by high rates of infection and diarrhea, the protective effects of breastfeeding against infectious gastroenteritis reduces growth faltering and can thus lead to higher mean weight gains of breastfed babies than of infants not receiving human milk [45–47]. With
adequate hygienic conditions, however, infants fed conventional infant formula achieve a greater gain of bodyweight and weight-for-length during infancy and early childhood than breastfed infants [48, 49]. In a systematic review of 19 studies in affluent populations, the cumulative difference in bodyweight was as large as 400 g at one year of age in infants breastfed for 9 months, and even 600–650 g in infants breastfed for 12 months [50].

Given these marked differences in early growth pattern, we explored the potential effects of these early growth differences on later body size. We studied the relation of breastfeeding with later overweight and obesity risk in a cross-sectional survey in Bavaria, Germany [51]. Data on height and weight were obtained for 9,357 children participating in the obligatory school health examination. Previously breastfed children showed a lower prevalence of both overweight (9.2 vs. 12.6%) and obesity (2.8 vs. 4.5%) than formula-fed ones. Differences in social class or lifestyle did not explain the protective effect of breastfeeding. Children who had ever been breastfed showed a significantly reduced adjusted odds ratio (OR) for both overweight (OR 0.79, 95% CI: 0.68–0.93) and obesity (OR 0.75, 95% CI: 0.57–0.98) as compared to those who were never breastfed. The adjusted ORs showed a significant inverse dose-response relationship between duration of breastfeeding and both overweight and obesity, which is compatible with a causal effect of breastfeeding or breast milk components on obesity reduction (fig. 2).

Many other investigators also explored the relationship between breastfeeding and later obesity in different cohort studies. These have been evaluated in
several systematic reviews and meta-analyses [45, 46]. We performed a meta-
analysis of published epidemiological studies (cohort, case-control or cross-
sectional studies) that included only studies adjusting for at least three relevant
confounding factors (birthweight, parental overweight, parental smoking,
dietary factors, physical activity and socioeconomic status/parental educa-
tion) and assessed obesity at an age between 5 and 18 years [52]. Included
were 9 studies with more than 69,000 children. The result of the meta-
alysis showed breastfeeding associated with a significant reduction of the risk of obe-
sity in childhood in the fixed model (adjusted OR 0.78, 95% CI: 0.71–0.85). A
dose-dependent effect of breastfeeding duration on the prevalence of obesity
was reported in 4 of the 9 studies. Funnel plot regression gave no indication of
publication bias. Very similar results were published one year later by Harder
et al. [53] in a meta-analysis with different inclusion criteria and a much
larger number of studies evaluated. They found breastfeeding associated with
reduced pooled adjusted OR for later obesity of 0.75 (95% CI: 0.68–0.82) and
concluded that each additional month of breastfeeding resulted in 4% lower
obesity prevalence at later ages. In a further meta-analysis, Owen et al. [54]
confirmed a protective effect of breastfeeding in a meta-analysis based on an
even larger number of studies that met their inclusion criteria but reported
a smaller effect size (OR 0.87). In this analysis, 75% of the effect weight was
contributed by a single large study from the US Women, Infants and Children
program on low-income women and children [17]. This study included a
specific US population with a high degree of mixed feeding that might have
led to results which are not representative of other breastfed populations. A
more recent cluster randomized study did cast doubt on the protective effect
of breastfeeding on obesity risk. The trial had been performed in hospitals in
Belarus that were either assigned to enhanced breastfeeding promotion, or to
no active intervention [55]. Whereas the intervention achieved a significantly
longer duration of breastfeeding, there was no effect on obesity prevalence
at the age of 6.5 years. However, it is important to note that this trial did not
have sufficient statistical power to answer the question of a protective effect of
breastfeeding relative to formula feeding, because rates of breastfeeding were
relatively similar in the intervention and control groups, and the prevalence of
obesity was low in this population [56]. Of interest, Beyerlein and von Kries
[56] and Beyerlein et al. [57] found evidence that breastfeeding reduces par-
ticularly the proportion of subjects with a high BMI at later ages, while having
little effect on the mean BMI.

We conclude that the totality of the evidence shows breastfeeding associated
with a moderate but consistent protective effect against later obesity. Clearly,
these findings should encourage the promotion, protection and support of
breastfeeding, and of ethical approaches to the marketing of breast milk substitu-
tutes such as infant formulas and follow-on formulas, which do not undermine
breastfeeding [58, 59].
Mechanisms of Protective Effects of Breastfeeding: The ‘Early Protein Hypothesis’

Understanding the underlying mechanisms as to how breastfeeding protects against later obesity could strengthen the conclusions on protective effects of breastfeeding, and it might help to extend protective effects to infants that are not breastfed for longer time periods by improving practices of feeding formula or complementary foods. Very many factors differ between breastfeeding and bottle feeding; therefore, numerous different hypotheses can be raised here [17].

We have previously proposed that the greater weight gain in formula-fed infants, relative to breastfed infants, is at least partly caused by the different intakes of metabolizable protein [50]. We explored the hypothesis that the usually 55–80% higher protein supply to formula-fed babies, as compared to breastfed infants [60, 61], could enhance both early weight gain and later obesity risk (the ‘Early Protein Hypothesis’) [62]. As described above, amino acids stimulate the secretion of insulin and IGF-I and positively activate mTORC1; thus, a high protein intake in excess of metabolic requirements may increase the concentrations of insulin and IGF-I in the circulation (fig. 3). Epidemiological studies actually found high protein intakes in infancy and the 2nd year, but not of energy, fat or carbohydrates, predictive of an early occurrence of the adiposity rebound and a high BMI in childhood [63–67].

Fig. 3. The Early Protein Hypothesis suggests that a dietary protein supply to infants in excess of their metabolic requirements will lead to increased plasma and tissue concentrations of insulin-releasing amino acids and an enhanced secretion of insulin and IGF-I, which in turn will enhance early weight gain, adipogenic activity and long-term obesity risk. Redrawn after Koletzko et al. [23].
We tested the Early Protein Hypothesis in a randomized clinical trial, the European Childhood Obesity Project [24] performed as part of a European Commission-funded research collaboration [68]. This multicentric RCT was set up in study centers in five European countries (Belgium, Germany, Italy, Poland, Spain). Eligible for study participation were apparently healthy, term infants born from uncomplicated, singleton pregnancies. Formula-fed infants received exclusively one of the two randomized formulas at a mean age of 2 weeks after birth and no later than at the end of the 8th week of life. Breastfed children had to be exclusively breastfed for the first 3 months. Infant formulas were replaced by follow-on formulas from the 5th month of age onwards.

The lower protein (LP) and higher protein (HP) infant and follow-on formulas had an identical energy density achieved by adaptation of the fat content, whereas the protein contents were 1.8 g protein/100 kcal versus 2.9 g protein/100 kcal in the infant formulas and 2.2 g protein/100 kcal versus 4.4 g protein/kcal in the follow-on formulas (table 1). The relative contents of amino acids did not differ between all four formulas, e.g. branched-chained amino acids made up 23% of the protein content in all four formulas (table 1).

A reference group of 619 breastfed infants was recruited, of whom 298 children could be followed until the 24 months visit. Complete anthropometric follow-up data at 24 months were available for 313 LP infants (follow-up rate = 58%) and 323 HP infants (59%). The median age at the baseline visit was 16 days (interquartile range, IQR: 2–29 days). The protein intake was significantly different between the two formula groups at all time points up to 12 months of age but not thereafter. The difference ranged between 5.5 g per day (95% CI: 5.1–5.9) in the first month to 8.5 g (7.8–9.3) at 6 months. Energy intake in the LP and HP formula groups was identical at 3, 12, and 24 months, but was slightly higher (24 kcal, 95% CI: 6–43) at 6 months of age in the LP formula group.

Differences in weight and weight-for-length between the formula groups emerged at 6 months of age and remained relatively stable thereafter with a decreasing tendency towards the end of the study. At 24 months of age, length was not different between the intervention groups. The mean weight attained at 24 months was 12.42 and 12.60 kg for the LP and HP groups, respectively. HP led to a significantly higher BMI than LP during the intervention period from 6 months onwards as well as after the end of the intervention (fig. 4). Of interest, the BMI in the LP group was identical to the breastfed group at 2 years of age. The effect of the intervention was not different among the countries for any of the analyzed anthropometric measures. In addition to total body growth, also a significant effect on kidney growth was found [69]. We estimated the potential impact of the reduced protein intake in infancy on obesity in adolescence based on the observed effects of change in weight-for-length gain during the first 2 years of life on later obesity in large prospective cohort studies, and we calculated an expected reduction of obesity prevalence
at 14–16 years by 13% [24]. The actual effects of the intervention after the early toddler age are currently being explored in a longer term follow-up study.

### Biochemical and Endocrine Markers

To explore our underlying hypothesis that the effect of dietary protein on growth and obesity risk is mediated by amino acid concentrations, insulin and IGF-I, we performed respective analyses in venous blood and in urine samples that were obtained from participating infants at the age of 6 months and were analyzed in one central laboratory [70].

<table>
<thead>
<tr>
<th></th>
<th>Infant formula</th>
<th>Follow-on formula</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LP</td>
<td>HP</td>
</tr>
<tr>
<td>Energy, g/100 ml</td>
<td>69.9</td>
<td>69.8</td>
</tr>
<tr>
<td>Proteins, g/100 ml</td>
<td>1.25</td>
<td>2.05</td>
</tr>
<tr>
<td>Percent energy</td>
<td>7.1</td>
<td>11.7</td>
</tr>
<tr>
<td>Lipids, g/100 ml</td>
<td>3.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Carbohydrates, g/100 ml</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Glutamic acid, mg/100 ml</td>
<td>286</td>
<td>473</td>
</tr>
<tr>
<td>Proline, mg/100 ml</td>
<td>135</td>
<td>223</td>
</tr>
<tr>
<td>Leucine, mg/100 ml</td>
<td>119</td>
<td>197</td>
</tr>
<tr>
<td>Lysine, mg/100 ml</td>
<td>94</td>
<td>155</td>
</tr>
<tr>
<td>Asparagine, mg/100 ml</td>
<td>89</td>
<td>147</td>
</tr>
<tr>
<td>Valine, mg/100 ml</td>
<td>84</td>
<td>139</td>
</tr>
<tr>
<td>Isoleucine, mg/100 ml</td>
<td>77</td>
<td>128</td>
</tr>
<tr>
<td>Serine, mg/100ml</td>
<td>71</td>
<td>118</td>
</tr>
<tr>
<td>Tyrosine, mg/100 ml</td>
<td>62</td>
<td>103</td>
</tr>
<tr>
<td>Phenylalanine, mg/100 ml</td>
<td>58</td>
<td>97</td>
</tr>
<tr>
<td>Threonine, mg/100 ml</td>
<td>56</td>
<td>92</td>
</tr>
<tr>
<td>Arginine, mg/100 ml</td>
<td>50</td>
<td>74</td>
</tr>
<tr>
<td>Alanine, mg/100 ml</td>
<td>42</td>
<td>69</td>
</tr>
<tr>
<td>Histidine, mg/100 ml</td>
<td>32</td>
<td>53</td>
</tr>
<tr>
<td>Glycine, mg/100 ml</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>Tryptophane, mg/100 ml</td>
<td>22</td>
<td>29</td>
</tr>
<tr>
<td>Cystine + methionine, mg/100 ml</td>
<td>40</td>
<td>66</td>
</tr>
</tbody>
</table>

Adapted from Koletzko et al. [24] and Socha et al. [71].
Median total amino acid serum concentrations were slightly higher in the HP group (3,041 μmol/l, IQR 2,679–3,394) than in the LP group (2,841 μmol/l, IQR 2,523–3,186, p < 0.001). Particularly large group differences were found for the branched-chain amino acids valine (+42% in HP), leucine (+37%) and isoleucine (+32%; table 2). The concentrations of all other essential amino acids were at least 10% higher in HP than in LP. In contrast, non-essential amino acids were either not different or even lower in the HP group, with the exception of tyrosine and asparagine which were both significantly higher. Interestingly enough, the total non-essential amino acid concentrations were not higher but significantly lower in the HP group (p = 0.001) [70].

Serum urea concentrations were significantly higher in infants fed HP than in those fed LP formulas (table 3). In the HP group, the serum concentrations of total IGF-I and free IGF-I were about 40% higher than in the LP group (table 3), while IGF-BP2 concentrations were about 30% lower. The HP group also showed a higher urinary C-peptide concentration and C-peptide/creatinine ratio, indicating enhanced insulin secretion, as well as a significantly lower serum glucose concentration (table 3).

Both formula groups showed differences to the breastfeeding group. Generally, parameters of the IGF axis, C-peptide and amino acids were more similar between the LP group and the breastfed group. Total IGF-I, free IGF-I, and IGF-BP3 levels were all significantly lower – up to almost 60% – in the breastfed than in the formula groups (table 3) [70]. Serum glucose, urinary C-peptide and the C-peptide/creatinine ratio all differed significantly between

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Fig. 4. BMI SDS from birth to age 2 years in subjects participating in the European Childhood Obesity Project fed breast milk, or randomized to receive for the first year of life formulas with LP or HP contents. Formula-fed infants in the HP group showed higher BMI values than breastfed infants in infancy and at 2 years of age. The group randomized to LP had significantly lower BMI levels than the HP group, and LP normalized BMI levels at age 2 years as compared to breastfed subjects. Drawn from data of Koletzko et al. [24].
Table 2. Serum amino acid (AA) concentrations in infants aged 6 months fed HP and LP formula, and in breastfed infants (BF)

<table>
<thead>
<tr>
<th></th>
<th>LP</th>
<th>HP</th>
<th>p value</th>
<th>BF</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(HP vs. LP)</td>
<td></td>
</tr>
<tr>
<td><strong>Essential amino acids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ILE, μmol/l</td>
<td>64 (50, 80)</td>
<td>85 (62, 114)</td>
<td>&lt;0.001</td>
<td>58 (46, 74)</td>
</tr>
<tr>
<td>LEU, μmol/l</td>
<td>120 (98, 143)</td>
<td>165 (124, 212)</td>
<td>&lt;0.001</td>
<td>106 (90, 133)</td>
</tr>
<tr>
<td>LYS, μmol/l</td>
<td>166 (134, 197)</td>
<td>197 (156, 248)</td>
<td>&lt;0.001</td>
<td>145 (121, 184)</td>
</tr>
<tr>
<td>MET, μmol/l</td>
<td>31 (26, 39)</td>
<td>35 (26, 46)</td>
<td>&lt;0.001</td>
<td>27 (22, 35)</td>
</tr>
<tr>
<td>PHE, μmol/l</td>
<td>72 (61, 83)</td>
<td>84 (70, 100)</td>
<td>&lt;0.001</td>
<td>61 (48, 74)</td>
</tr>
<tr>
<td>THR, μmol/l</td>
<td>126 (101, 154)</td>
<td>142 (118, 173)</td>
<td>&lt;0.001</td>
<td>119 (92, 150)</td>
</tr>
<tr>
<td>TRP, μmol/l</td>
<td>56 (47, 67)</td>
<td>67 (54, 82)</td>
<td>&lt;0.001</td>
<td>60 (50, 74)</td>
</tr>
<tr>
<td>VAL, μmol/l</td>
<td>214 (182, 247)</td>
<td>304 (241, 376)</td>
<td>&lt;0.001</td>
<td>172 (143, 208)</td>
</tr>
<tr>
<td><strong>Non-essential amino acids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALA, μmol/l</td>
<td>440 (346, 526)</td>
<td>420 (349, 517)</td>
<td>0.304</td>
<td>430 (355, 495)</td>
</tr>
<tr>
<td>ARG, μmol/l</td>
<td>115 (97, 137)</td>
<td>110 (91, 128)</td>
<td>0.038</td>
<td>113 (91, 129)</td>
</tr>
<tr>
<td>ASN, μmol/l</td>
<td>54 (45, 64)</td>
<td>58 (47, 68)</td>
<td>0.015</td>
<td>52 (45, 64)</td>
</tr>
<tr>
<td>ASP, μmol/l</td>
<td>25 (17, 35)</td>
<td>27 (19, 35)</td>
<td>0.143</td>
<td>26 (18, 38)</td>
</tr>
<tr>
<td>GLN, μmol/l</td>
<td>605 (542, 683)</td>
<td>556 (490, 613)</td>
<td>&lt;0.001</td>
<td>664 (573, 748)</td>
</tr>
<tr>
<td>GLU, μmol/l</td>
<td>122 (95, 168)</td>
<td>115 (88, 172)</td>
<td>0.179</td>
<td>130 (90, 193)</td>
</tr>
<tr>
<td>GLY, μmol/l</td>
<td>267 (217, 319)</td>
<td>230 (199, 273)</td>
<td>&lt;0.001</td>
<td>220 (185, 264)</td>
</tr>
<tr>
<td>HIS, μmol/l</td>
<td>105 (88, 123)</td>
<td>107 (93, 124)</td>
<td>0.215</td>
<td>88 (74, 105)</td>
</tr>
<tr>
<td>SER, μmol/l</td>
<td>161 (138, 194)</td>
<td>159 (140, 189)</td>
<td>0.750</td>
<td>187 (156, 207)</td>
</tr>
<tr>
<td>TYR, μmol/l</td>
<td>83 (70, 103)</td>
<td>101 (76, 125)</td>
<td>&lt;0.001</td>
<td>66 (54, 80)</td>
</tr>
</tbody>
</table>

Adapted from Socha et al. [71]. Values are expressed as median (IQR, 25th, 75th quartile).

a p < 0.05, LP vs. BF; b p < 0.01, LP vs. BF; c p < 0.001, LP vs. BF; d p < 0.05, HP vs. BF; e p < 0.01, HP vs. BF; f p < 0.001, HP vs. BF.

the breastfed and the formula groups (table 3). Essential amino acids, especially branched-chain amino acids, were lower in the breastfed than in the LP group, whereas non-essential amino acids had about the same level.

Total IGF-I was found positively correlated with weight-for-length at 6 (fig. 5), 12, and 24 months, whereas C-peptide showed no association with weight-for-length.

**Conclusions**

Breastfeeding or formula feeding and dietary protein supply in infancy were found to markedly affect the metabolic and endocrine response of infants, and their growth. HP intakes increase the plasma levels of essential amino acids, especially branched-chain amino acids, serum concentrations of total and
free IGF-I, and urinary C-peptide levels which reflect increased insulin secretion, while the serum glucose level was lowered. Using infant formula with LP content results in a more similar – but not equal – metabolic and endocrine response as compared to breastfed infants, while it normalizes weight and BMI of formula-fed babies relative to healthy breastfed subjects during the first 2 years of life.

The observed marked effects of formula protein contents on total and free IGF-I agree with earlier observations of lower IGF-I levels in breastfed compared to formula-fed infants, and in some studies with varying protein intakes, as reviewed by Socha et al. [71]. The observed correlation of IGF-I levels with weight-for-length leads us to conclude that IGF-I is a key driver of weight gain during infancy, which clearly can be modulated to a biologically relevant extent by dietary composition. In addition to modulating growth, elevated IGF-I levels in infancy may also have further long-term effects. Formula feeding, HP intakes, and higher IGF-I levels in infancy have been associated with lower IGF-I levels in later life [72–75], whereas breastfeeding is associated with lower IGF-I in infancy but higher IGF-I in later childhood [72]. In healthy adults, a lower IGF-I concentration has been associated with an increased risk of both ischemic heart disease and diabetes [76] as well as with increased incidence of malignancies such as prostate and breast cancer [77]. Therefore, programming of the IGF-I axis through early nutrition in infancy may have a considerable impact on the later risk not only of obesity but also of other

### Table 3.

Serum concentrations of free and total IGF-I IGF-BP2 and IGF-BP3, glucose and urea, and of urinary C-peptide in infants on LP and HP and in BF infants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LP</th>
<th>HP</th>
<th>P (HP vs. LP)</th>
<th>BF</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I free, ng/ml</td>
<td>0.43 (0.27, -0.77)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.60 (0.34, 1.11)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>0.31 (0.21, 0.48)</td>
</tr>
<tr>
<td>IGF-I total, ng/ml</td>
<td>34.7 (17.7, 57.5)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>48.4 (27.2, 81.8)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>14.1 (5.1, 33.2)</td>
</tr>
<tr>
<td>IGF-BP2, ng/ml</td>
<td>1,090 (865, 1,438)</td>
<td>765 (575, 1,013)</td>
<td>&lt;0.001</td>
<td>1,370 (1,055, 1,740)</td>
</tr>
<tr>
<td>IGF-BP3, ng/ml</td>
<td>2,908 (2,449, 3,440)</td>
<td>2,969 (2,538, 3,483)</td>
<td>0.248</td>
<td>2,454 (1,984, 2,794)</td>
</tr>
<tr>
<td>C-peptide/creatinine ng/mg</td>
<td>107.3 (65.2, 194.7)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>140.6 (80.0, 203.8)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.030</td>
<td>57.0 (27.3, 119.3)</td>
</tr>
<tr>
<td>C-peptide, ng/ml</td>
<td>19.5 (9.4, 34.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26.9 (13.3, 45.6)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.002</td>
<td>9.3 (3.5, 20.1)</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>85 (77, 93)</td>
<td>83 (77, 89)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.022</td>
<td>86 (79, 93)</td>
</tr>
<tr>
<td>Urea, mg/dl</td>
<td>18 (14, 21)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29 (20, 36)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>11 (8, 16)</td>
</tr>
</tbody>
</table>

Adapted from Socha et al. [71]. Values are expressed as median (IQR, 25th, 75th quartile).

<sup>a</sup> p < 0.001, LP vs. BF; <sup>b</sup> p < 0.001, HP vs. BF.
adult diseases [72]. While lowering protein supply decreased IGF-I levels, these still remained far higher than the levels observed in breastfed babies. Thus, further exploration of the regulators of the IGF-I axis in early life is needed, including the investigation of the effects of IGF gene variants on IGF-I and its binding proteins, and their interaction with nutrition and growth.

Given that insulin plays a central role in metabolic regulation, IGF-I transcription and enhanced body fat deposition, the observed increased C-peptide levels by HP intake might also induce lasting effects on growth and health outcomes. Attenuation of the elevated insulin secretion though optimized early nutrition, such as LP intake in formula-fed babies, seems desirable. In addition to reducing protein supply with infant formula, the use of unmodified cows’ milk as a drink during the first year of life, which provides very high protein intake, should be discouraged [78].

The available data should prompt enhanced efforts to actively promote, protect and support breastfeeding. For those infants that are not breastfed or not fully breastfed, we consider the use of infant formulas with reduced protein content but high protein quality preferable.

Appendix

The European Childhood Obesity Project Study Group
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Genome-Wide Association Studies of Human Growth Traits

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Abstract
Despite the high heritability of human growth traits, until recently little was known about the underlying genes and genetic variants which explain normal variation of growth. In the past few years, genome-wide association studies have successfully identified hundreds of genetic variants that are associated with human growth traits. These variants have implicated many novel genes in the regulation of birthweight and pubertal timing through to final adult height, and are providing new insights into the biology of growth. For example, 180 genetic loci have been robustly shown to influence variation in final adult height. Despite this success, the effect sizes of these variants are small and, even in combination, have left the majority of heritable genetic variation of growth traits unexplained. In this review, I discuss the successes of the genome-wide association approach and some of the novel insights into the biology of growth that have come from these studies. I will also discuss what these studies have not told us and what the future holds for genetic studies of human growth.

Introduction
It has long been known that variation in the rate and extent that humans grow is largely due to inherited genetic variation. The proportion of variation explained by heritable factors, as opposed to environmental factors, for different aspects of growth range from around 40% for birthweight [1] to around 80% for adult height [2, 3]. Until recently, however, the specific genetic variants that explain this heritability were largely unknown.

There has been substantial success in identifying the specific genetic mutations which cause some extreme growth syndromes. For example, loss-of-function
mutations of the *IGF1R* gene (insulin-like growth factor-I) have been shown to cause intrauterine and postnatal growth retardation [4]. Another example comes from Rauch et al. [5] who demonstrated that loss of function mutations of *PCNT*, the gene encoding pericentrin, which is involved in centromere function in the cell cycle, are a cause of primordial dwarfism. The number of such genes implicated in extreme growth is large and growing (see OMIM, http://www.ncbi.nlm.nih.gov/omim). However, the genetic mutations that explain these extremes of growth are rare in the population and cannot explain normal variation in growth, and until recently there were no common genetic variants that were robustly shown to influence variation in any growth-related trait. This has all changed with the advent of genome-wide association (GWA) studies.

The traditional linkage and candidate gene approaches that are extremely powerful in identifying rare, highly penetrant mutations causing disease were not successful for identifying the variants that explain normal variation in growth. The linkage approach has not been a success because, compared with association methods, it is not a powerful approach to detect variants of small effect size, even when large sample sizes are used [6]. Whereas the candidate gene approach is unsuccessful because of a combination of the large number of potential candidate genes (there are ~20,000 genes in the human genome, many potentially involved in growth and development processes), and also the small sample sizes that many studies used (typically just a few hundred samples, when many thousands are required). Instead, the development of genotyping microarray chips, which allow most of the common genetic variation (that is the >5 million variants which occur in the population at >5% frequency) to be assayed simultaneously in an individual, combined with very large sample sizes and collaborative efforts has led to the large-scale GWA study approach. These efforts have started to uncover the genetic variants that explain normal variation in growth.

In this review, I will discuss the recent successes of GWA studies for human growth traits. I will describe the hundreds of loci that have been identified for phenotypes ranging from birthweight to final adult height. I will discuss what these findings have told us about the genetic architecture of these traits as well as the novel biological insights that have been gained. I will also discuss what these studies have not told us – there is a large fraction of heritability that remains to be explained – and what the future directions are for genetic studies of growth.

**The First Successes for GWA Studies of Growth Traits – FTO and HMGA2**

In 2007, as part of the Wellcome Trust Case Control Consortium (WTCCC) [7], we reported a GWA study of type 2 diabetes, where we identified seven loci where common genetic variants influenced risk of the disease [8]. We went on to show that one of these genes, *FTO*, was increasing risk of type 2 diabetes.
through a primary impact on increasing weight [9]. We demonstrated that the effect was seen from the age of 7, and was specifically due to an increase in fat mass. The FTO finding provides an excellent example of the power of GW A studies to identify new biology. Before our study, FTO was a poorly described gene in an unknown pathway. A large amount of work has since been put into understanding the function of FTO and how it is affecting weight. It has been shown, for example, that it is a nucleic acid demethylase [10]. However, the underlying biological mechanism is still not entirely clear. Inactivation of FTO in a mouse model produced mice that were lean, primarily due to an effect on basal metabolic rate [11], while a study which overexpressed FTO in mice suggested a primary effect on appetite [12]. The appetite effect is supported by human studies [13–15]. Recently, in a longitudinal follow-up study of children from early infancy until age 13 years, the FTO variant that increases BMI in adults was shown to have the opposite effect in infants below the age of 2.5 years [16]. Further elucidation of the role of FTO during development is likely to provide important new insights into the biology of obesity and growth.

The successful identification of genes for type 2 diabetes and BMI spurred on efforts to identify genes for other traits. Adult height is a classic genetic trait which was used as a model trait by Galton [17] and Fisher [18] in the early days of human genetics. It is a model trait because of its high heritability and because it is easily, accurately and widely measured. We therefore performed an initial GW A study of adult height in 2,000 individuals (from the same WTCCC type 2 diabetes study) and identified no significant associations. It was only when we meta-analyzed our GW A association data with 3,000 individuals from the Diabetes Genetic Initiative study, that a significant association was observed [19]. The variants that associated with height occurred in the HMGA2 gene, which is a high mobility group protein involved in chromatin remodeling. HMGA2 was an excellent candidate to influence height because the knockout of this gene causes the pygmy mouse phenotype [20], and an inversion of this gene was shown to cause an 8-year-old boy to be more than 5 standard deviations taller than expected for his age [21]. The effect size of the HMGA2 variant was small – homozygotes for the variant allele, which has a frequency of ~50% in Europeans, were on average only a 1 cm taller than the reference homozygotes, and the variant explained only 0.3% of the variation in height. There were clearly many more variants contributing to normal variation in height.

**Increasing Sample Size by Collaboration and Meta-Analysis Identifies Hundreds of Loci for Adult Height and Other Anthropometric Traits**

The only way to find these additional loci was to increase the sample size of GW A studies. We therefore collaborated with other groups from the WTCCC and increased our discovery sample size to 13,665 individuals and used 16,482
for replication of the most associated variants. This led to the identification of 19 further loci convincingly associated with adult height. Other groups were performing similar studies [22, 23], and in 2008 a total of 52 loci were reported to be associated with final adult height. In combination, however, these loci explained only ~5% of the normal variation in European populations. It was clear that even further expansion and combination of data would yield even more associated loci, and so the GIANT (Genetic Investigation of Anthropometric Traits) consortium was set up. The GIANT consortium analysis for height included 183,727 participants from 45 individual GWA studies (from a range of different disease areas) [24]. Analysis of this huge number of individuals led to the identification of 180 height-associated loci. In combination, these variants explained ~10% of the population variation in final adult height (and so ~12% of the heritable variation).

The biological insights that can be gained from GWA studies are limited by an inability to pinpoint the exact causal mutation due to correlation with nearby variants that are co-inherited. This correlation is useful in that it allows us to identify the associations in the first place (by reducing the number of variants that need to be genotyped); but, once we have identified the association it prevents us from, at least genetically, narrowing down the causal variant from the many other, often tightly, linked, variants. So much further work is needed to fine-map the associations identified from GWA studies to provide the new insights into the biology of growth that these GWA studies have promised. Nevertheless, we demonstrated that there is an overrepresentation of strong candidate genes at the 180 height-associated loci (i.e. those where rare, severe, mutations cause extreme growth), and that the loci we have identified tend to contain genes which are biologically connected and which cluster in biological pathways. These pathways are both known and novel and include the hedgehog signaling, growth hormone and histone modification pathways [24].

While GWA studies for height have been particularly successful, a similar pattern has been observed for other growth traits. In addition to height, the GIANT consortium also analyzed other anthropometric phenotypes, including BMI and waist circumference. For BMI, 32 associated loci were recently reported [25]. These variants, however, account for only ~1% of the population variation in BMI – with FTO accounting for the majority of this. Variants associated with waist circumference (independently of BMI) have also been identified – and interestingly strong sex-specific differences were observed [26], whereas for height and BMI no such gender interactions were found [24, 25].

GWA Studies of Early Growth

In addition to adult phenotypes, substantial effort has been put into trying to map genes for earlier stages of growth. For example, there has been recent success in identifying genes for birthweight. Freathy et al. [27] performed a GWA
study in 10,623 children, and identified two loci strongly associated with birthweight. Interestingly, one of these, ADCY5, is also a variant associated with type 2 diabetes. This fits with earlier work showing that genetic variants that associate with reduced birthweight also increase risk of type 2 diabetes [27, 28], and is consistent with the fetal insulin hypothesis proposed by Hattersley and Tooke [29] that states that the strong epidemiological correlation between lower birthweight and increased risk of adult-onset diabetes could, at least partially, be explained by a shared genetic cause rather than the fetal programming proposed by Barker [30].

So far, none of the variants associated with adult height have been robustly associated with birthweight or length. Although, a recent study suggests that it is likely that a subset of the 180 height-associated variants will affect birth length and that, in combination, they explain more of the variation in growth as age increases (for example, explaining 5% of population variation of height at age 10, compared to 10% of adult height) [31]. It will be interesting to observe in future studies what the overlap between variants associated with height and fetal and postnatal stages of growth is – and it is likely that at least some of the adult height variants will be primarily fetal growth genes.

**GWA Studies of Pubertal Growth**

GWA studies of later stages of growth, in particular aspects of puberty, have also yielded associations. One particularly interesting association from these studies was at the LIN28B locus [32, 33]. LIN28B is a regulator of microRNA processing, and the same variant of this gene was also shown to be associated with adult height – with the allele that associates with earlier age at menarche associated with shorter height. Ong et al. [33] went on to show that this is a pubertal timing variant in both sexes. The allele that reduces menarche age in girls was also associated with earlier breast development, and in boys was associated with earlier voice breaking. Widen et al. [34] performed a GWA study of growth trajectories in 5,038 Finnish children and came to similar conclusions, and also found a second, independent signal at the same locus which appears to be a sex-specific effect. In this case, the causality of the LIN28B gene at this locus is supported by the mouse knockout of LIN28A (a homolog of LIN28B) which demonstrates consistent effects on reduced growth and early puberty phenotypes [35].

As with other traits, a larger scale meta-analysis (including 87,802 women) yielded further associations, with a total of 32 loci now being robustly associated with age at menarche [36]. These loci contain genes that fall into pathways related to energy homeostasis (BSX, CRTC1 and MCHR2), hormonal regulation (INHBA, PCSK2 and RXRG) pathways and coenzyme A and fatty acid biosynthesis. The strongest overlap, however, was for genes which had previously been reported to be associated with BMI – for example, the allele that is strongly
associated with increased BMI at the \textit{FTO} locus is associated with reduced age at menarche, and presumably earlier puberty. This pattern was seen across all the known BMI loci, except for the \textit{MC4R} locus. \textit{MC4R} primarily influences weight through increasing muscle mass, and this suggests that the effect of these variants on reducing age at menarche is primarily through an effect on fat mass. This is consistent with earlier studies demonstrating that increased adiposity reduces time to puberty for girls [37]. The association of the height loci with age at menarche was more complex, with some associations (such as the \textit{LIN28B} locus) having a direction consistent with epidemiological studies (earlier menarche is associated with reduced height), but other loci had the opposite direction of effect [36].

\textbf{The Genetics of Growth Is More Complex Than Previously Appreciated}

The large number of loci identified from these GWA studies of growth allows us to make some general conclusions about the genetic architecture of normal growth. The most obvious conclusion is that a very large number of genes and variants are responsible for normal variation in development. That multiple variants influence height is not surprising – in 1918 Ronald Fisher in his classic paper showed that this was likely the case [18]. What is surprising is the sheer number of variants. We have estimated that 697 variants would be identified with a sample size of 500,000 but that this would only explain \textasciitilde 20\% of heritability [24] – this indicates that many thousands of variants in many thousands of genes may ultimately be responsible for normal variation in height – and millions of individuals would be needed to identify them all. In hindsight, this is perhaps not surprising given that adult height is a combination of a huge number of developmental and other processes.

\textbf{What GWA Studies Have Not Told Us – The Missing Heritability}

GWA studies have been a success – in many cases they have identified the first genetic variants to influence variation of a common disease or trait (a full list of GWA study associations across all traits is available at http://www.genome.gov/26525384), which have provided new insights into biology and pathophysiology (e.g. \textit{FTO} and \textit{LIN28B}). The follow-up to these studies is likely to provide many new insights as functional variants and genes involved in these traits are fine mapped. Although, given the difficulty of these efforts and the large number of loci, it may be that the focus will be on identifying novel pathways in which genes at these loci cluster.

One aspect that has been disappointing is the small effect size of the variants identified and the limited amount of heritability that they explain. This means
that the clinical utility of these markers for prediction is limited for most traits. For example, for height it has been shown that knowing parental height is by far a better way of predicting a child’s height than using variants identified from GWA studies – and it is likely to be the case for some time to come [38]. The relatively small amount of heritability explained also means that there is a lot of biology left to be understood. So, one of the major questions in complex traits genetics currently is: where is this missing heritability? There are several possible sources [39]. It could be that common variants will explain a substantial amount of the missing heritability – it is just that exceptionally large (i.e. millions of individuals) samples will be needed to detect these variants. The fall-off in effect sizes of newly discovered variants as larger sample sizes are analyzed suggests that there is a limit to the amount that common genetic variants can explain with reasonable sample sizes (see fig. 1). Although, work by Yang et al. [40] suggests that at least 45% of the heritability of height can be explained by genetic variants captured on current versions of genotyping chips. However, even if this proves true, this is likely to leave a substantial amount of heritability unexplained.

Another possibility is that lower frequency (0.5–5% population frequency) and rare (<0.5%) variants may explain much of the remaining heritability. These lower frequency variants are not well captured on current versions of genotyping chips (which have focused on variants with frequencies >5%). Studies in type 1 diabetes, where low frequency, but reasonably penetrant (odds ratios ~3) variants were found in the IFIH1 gene using a next generation sequencing approach, demonstrate this type of variant exists and demonstrates that it can be used to identify conclusively the gene at an associated loci [41]. We can now systematically test for association for this type of variant because of the

![Fig. 1. Cumulative proportion of variation explained for the 180-height associated SNPs. The data are based on stage 2 of the GIANT height study [24].](image)
huge leaps in sequencing technologies that have occurred in the past few years. These technologies now allow a high-quality whole human genome sequence to be completed within a week and for less than USD 5,000 [42]. This is compared to the 10 years and USD >1 billion required to complete the reference sequence just 10 years ago [43]. It is also possible to sequence just the 1% of the genome which codes for proteins using sequence capture methods [44]. This whole exome sequencing approach allows for a more economic analysis of the most readily interpretable regions of the genome – with prices USD <1,000 per exome. With more and more groups performing these types of study, the focus will move away from GWA chips and towards a next generation of GWA studies using whole genome and whole exome sequencing data. It is likely that cohorts of the size currently used for GWA will be needed to fully exploit these data, but there is hope that this will lead many new exciting discoveries and fill in much of the gap in unexplained heritability.

While rare variants may be of major importance, other explanations of the missing heritability include gene-gene and gene-environment interaction, structural variants and epigenetic effects. No evidence has so far been found for gene-gene interaction for any growth-related trait. For example, we assessed all 180 height-associated loci for interaction, and found no evidence of any deviation from an additive effects model [24]. Although, even though we analyzed 100,000 individuals, this may be due to lack of power due to subtle interaction effects, or that interacting variants do not present with strong main effects. Structural variants will almost certainly be a source of the missing heritability – and the detection of these should be facilitated by next-generation sequencing technologies. While common copy number variants are unlikely to have a disproportionate role (as demonstrated by the recent WTCCC study [45]), rarer structural variants will almost certainly play a role. One recent example comes from the demonstration that a low-frequency 600-kb deletion of 16p11.2 causes obesity, whereas duplication of this region causes underweight [25, 46]. Epigenetic effects will also play a role. There is already an example of this from a parent of origin analysis reported by Kong et al. [47] that demonstrated that the effect of three type 2 diabetes variants was dependent on the parent from which the allele was inherited. The importance of each of these potential sources of the missing heritability will become clearer over the next few years.

Conclusions

GWA studies have been successful. They have identified the first common genetic variants associated with normal variation in growth. Based on these findings, new and important insights into the biology of growth have already been made – and more will come with ongoing and future follow-up studies. The associated variants have, however, left a substantial amount of heritable
variation unexplained. With developments in sequencing technologies and large-scale collaborations, genetic studies of growth should fill in this gap over the coming years.

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Discussion on Nutrition and Genetics

This first session of the Workshop focused on the drivers of growth in the form of nutritional and genetic influences with relevance to normal populations, while the second session focused on lessons from pathology. This first session included two outstanding presentations considering the nutritional influences on prenatal (Dr. Makrides) and postnatal (Dr. Koletzko) growth. This was followed by a presentation of the state-of-the-art in growth genetics and the lessons derived from genome-wide association (Dr. Weedon).

Nutrition

Dr. Makrides’ scholarly review summarized a number of trials that investigated the benefits of macronutrients or micronutrients – primarily long-chain polyunsaturated fat supplementation – on duration of pregnancy and birth size. A number of important themes emerged in the following discussion, several of which resonated with later discussions in this session and in the meeting as a whole.

Effectiveness of Clinical Trials

The complexity of conducting properly randomized and blinded clinical trials was highlighted and widely recognized, especially when the intervention can only be introduced at 20 weeks’ gestation as is the case in many of these trials. The need to recruit adequate numbers of participants especially in nutritional trials and the frequent need to exclude those already on some sort of supplement was also described. Nutritional influences in the first trimester might be predicted to have greater impact on developmental aspects and potentially on
the long-term consequences of impaired nutrition, but for practical reasons conducting such studies is clearly complex.

**Appropriate End Points**

A valuable point that emerged in the discussion was the appropriateness of using birthweight as the end point in this type of trial when what one is really interested in might be the long-term outcomes or cognitive development of the child. Is birthweight an adequate surrogate for these biologically more relevant end points? Clearly birthweight is a highly objective and easily measurable index for this type of study, but greater sophistication in this area would be highly desirable. Dr. Makrides reported that attempts were underway to assess cognitive and immunological outcomes in her current studies in recognition of this point, and others pointed out the feasibility of measuring body composition using DXA scans as an alternative end point.

In the second presentation Dr. Koletzko considered the influences of nutrition on postnatal growth, and presented the findings of a large randomized clinical trial conducted as part of the European Childhood Obesity project aimed at testing the ‘Early Protein Hypothesis’ comparing the effects of lower protein and higher protein infant formula feeds and breastfeeding. The lower protein formula group and the breastfed group had significantly lower parameters of the insulin and IGF-I axis, and at 12 months and beyond had lower BMI. Since this is predictive of later obesity, these interesting findings raise the prospect of an early life intervention having an effective part to play in the long-term prevention of obesity. Importantly, the negative value of high-protein formulas, which are still used in some parts of the world, were revealed.

The varied and wide-ranging discussion of this paper considered a number of aspects that are explained below.

**Mechanistic Aspects and the Endocrine Response to Infant Nutrition**

While the importance of the IGF-I and insulin axes was well recognized, the complexity of other hormonal contributors such as ghrelin, leptin and adipokines, and their potential role in appetite regulation was questioned. Interestingly, energy intake and, by implication, appetite were not influenced by high- or low-protein formulas. Others commented on the apparent absence of a relationship between the greater IGF-I in high-protein group and growth.

**Difficulties in Conducting Clinical Trials**

As with studies in prenatal nutrition, conducting large-scale trials in postnatal nutrition is not without difficulty. The attrition resulting from failure to comply with the feeding regimens as the trial progresses was acknowledged, as was the potential for this attrition to skew the socioeconomic status of the groups. These requirements underline the importance of obtaining sufficient numbers in conducting such trials with the need for effective collaboration.
Animal Models
A further point briefly touched on was the relatively poor exploitation of the lessons derived from nutritional studies in larger mammals compared to humans. A plea for greater communication between scientists and clinicians working in each of these areas was made.

Genetics

The session then moved on to consider the genetic contribution to growth with a presentation from Dr. Weedon of the application of modern genomic technologies to the question of adult height by means of genome-wide association studies. Most researchers would agree that the ability to conduct some of the more recent very large-scale genetic association studies in which hundreds of thousands of individuals have been phenotyped and genotyped is an outstanding organizational achievement. Undoubtedly, a driver for this is the failure to find significant genetic associations when smaller samples were used, essentially forcing clinical scientists to collaborate. Of importance for this is the need for the evolution of adequate academic recognition for participating in such studies – a state that has not been entirely achieved in all environments.

Dr. Weedon presented the findings of the GIANT consortium study which had identified 180 height-associated genes, each of which, perhaps disappointingly made a very small individual contribution to actual height and combined accounts for about 15% of height. While fascinating, there is little doubt that this has led to some disappointment that such massive studies have not revealed a greater effect size.

Heritability
Undoubtedly height is highly heritable. The best predictor of a child’s eventual height is still to measure the parental heights. Having said this, the change in height associated with population migration is well documented – the example of the Mayans moving to Florida that was discussed in greater detail in a later session was raised. Other forms of heritability were discussed. Mitochondrial DNA was proposed as one non-mendelian genetic effect that might have influence. The speaker pointed out that future whole-genome association studies would include the mitochondrial genome. Dr. Weedon had considered the probably fairly minimal effects of gene-gene interactions (epistasis) as an explanation for his findings, and others highlighted the potential for gene-environment interactions.

Transgenerational Epigenetic Inheritance
A further and currently highly topical influence was the concept of transgenerational epigenetic inheritance. This term describes the potential for an epigenetic mark – e.g. DNA methylation, to be passaged into subsequent generations, in
contrast to the general dogma that epigenetic marks are wiped away following fertilization of the egg. There is clear evidence that transgenerational epigenetic inheritance can occur both through the female and male lines, although it appears to be a very selective process applying to a limited number of well-studied animal models. It has to be recognized however that our understanding of ‘epigenetic’ processes is in its infancy. Only very recently, for example, has a novel mark – hydroxymethyl cytosine – been described, and the probability seems that drawing conclusions about the role of epigenetics in population growth mechanisms is premature.

Adrian J.L. Clark
IGF-I in Human Growth: Lessons from Defects in the GH-IGF-I Axis

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Abstract
The IGF system plays a critical role in all phases of human growth, including intrauterine, childhood and pubertal. The importance of IGF-I for both in utero as well as postnatal human growth is highlighted by rare human homozygous IGF1 mutations, which are characterized by intrauterine growth retardation (IUGR), microcephaly, mental retardation and severe postnatal growth failure. Clinical conditions of IGF-I resistance due to mutations in the IGF-I receptor (IGFIR) similarly lead to IUGR and postnatal growth retardation. Postnatal regulation of IGF-I production is predominantly GH dependent. Defects in the GH-IGF-I axis, including mutations in the GHR, STAT5B and IGFALS genes, lead to postnatal IGF deficiency and GH insensitivity. Patients are of normal birth size but present with severe postnatal growth failure, despite normal or elevated levels of GH. Other phenotypic features – immune deficiency for STAT5B defects and insulin insensitivity for IGFALS defects – are of note. Mutations identified have been predominantly recessive. The identification and assessment of genetic defects in the GH-IGF axis has greatly enhanced our understanding of the critical importance of IGF-I in human linear growth. Continued evaluations will facilitate better diagnosis and management of children presenting with abnormal growth and development.

Normal Human Growth Is Dependent on IGF-I

The IGF system plays a critical role in all phases of human growth, including intrauterine, childhood and pubertal. IGF-I, like the highly homologous IGF-II, is structurally similar to insulin, and is known to exert critical endocrine,
paracrine and autocrine effects on growth, differentiation and metabolism of normal and malignant cells. The importance of IGF-I for both in utero as well as postnatal human growth is highlighted by three convincing cases of rare human homozygous \textit{IGF1} mutations [1–3], which are characterized by intrauterine growth retardation and severe postnatal growth failure (height standard deviation scores, SDS, below –4.9). For the first reported case, subsequent treatment with recombinant IGF-I therapy improved linear growth [4, 5]. Phenotypic characteristics such as microcephaly, mental retardation and (for 2 of the 3 patients) sensorineural deafness, furthermore, implied that prenatal exposure to IGF-I is critical for brain development [1, 2]. It remains unclear how intrauterine IGF-I production is regulated, although both nutrition and insulin appear to play some role [6].

Postnatal production of IGF-I is predominantly GH dependent, supported by the clinical conditions of GH deficiency (GHD) and GH insensitivity (GHI), both of which lead to IGF-I deficiency (IGFD) with accompanying growth retardation (height SDS as low as –11). These patients were of normal size at birth, indicating that while GH is clearly important for postnatal growth, growth in utero is not dependent on GH. In addition to defects affecting IGF-I production, defects that affect IGF-I transport or action(s) also lead to growth failure. Evaluating molecular defects associated with GHI conditions has provided valuable insights into our understanding of the critical role of IGF-I in human linear growth, and is the focus in this present report.

\textbf{The Human GH-IGF-I Axis in Human Growth}

Pituitary-derived GH exerts its growth effects primarily by regulating the expression of IGF-I in both hepatic and non-hepatic tissues. GH action is initiated upon binding to cell surface GH receptor (GHR), a homodimeric transmembrane protein. The GH-GHR interaction induces signal transduction through recruitment and activation of the cytosolic Janus kinase 2 (JAK2). The complex of signaling pathways activated (fig. 1) include four STAT (signal transducer and activator of transcription) pathways (STAT1, -3, -5a and -5b), the MAPK (mitogen-activated protein kinase) and the PI3K (phosphoinositide-3 kinase) pathways. The signaling cascades culminate in the regulation of multiple genes, including \textit{IGF1}, \textit{IGFBP3} (IGF binding protein 3) and \textit{IGFALS} (acid labile subunit, ALS). Human mutations have been identified in a number of these intracellular components. Since other hormones and cytokines utilize the same signaling components, however, the pleiotropic effects often exhibited do not necessarily reflect consequences of a disrupted GH-IGF-I axis.

Hepatic-produced IGF-I circulates in ternary complex with IGFBP-3 and ALS, and is delivered to IGF-I-responsive cells and tissues. The mitogenic
IGF-I in Human Growth: Lessons from Defects in the GH-IGF-I Axis

The IGF1R precursor peptide is posttranslationally cleaved into α- and β-chains, and the final functional IGF1R is a tetramer (α₂β₂). The extracellular dimeric α₂ subunits are involved in ligand binding, while intrinsic tyrosine kinase activity is located within the β₂ subunits. The binding of IGF-I to IGF1R leads to receptor autophosphorylation and activation of multiple downstream signaling pathways, including the PI3K/AKT and MAPK/ERK pathways important for cell survival and cell growth. Human mutations in the IGF1R gene have been identified (see below), and all have been heterozygous (only one compound heterozygous reported), presumably because a total absence of functional IGF1R is embryonically lethal, as has been demonstrated in Igf1r⁻/⁻ null mouse models [7, 8].

**Defects in the GH-IGF Axis: What Gene Analyses Reveal**

Valuable insights into GH-induced regulation of IGF-I production have been provided by analysis of molecular defects identified in patients who are GHI. GHI patients differ from patients with GHD (not discussed in this report) in

Fig. 1. The GH-IGF-I axis. Mutations affecting IGF-I synthesis, transportation, and action are indicated.
that they do not respond to either endogenous or exogenous GH in terms of growth or metabolic changes. Serum concentrations of IGF-I, IGFBP-3 and ALS are usually significantly below the normal ranges and remain low even upon exogenous GH treatment. GHI patients who are IGF resistant, in contrast, exhibit normal to elevated IGF-I levels (see below).

**GHR Mutations Are Associated with a Range of Phenotypes**

The most common causes of IGFD and GHI are mutations in the *GHR* gene (5p13-12; OMIM No. 262500). Over 70 different mutations in more than 250 individuals have been identified since the first described cases in 1966 [9, 10] (fig. 2a). The majority of *GHR* mutations are recessive, with only three proven dominant negative mutations described [11–13].

Patients who carry *GHR* mutations are proportionally short, and, classically, also present with dysmorphic features, including prominent forehead, shallow orbits, hypoplasia of the nasal bridge, high-pitched voices, prematurely aged skin (fig. 2b). A study of craniofacial phenotype suggested those with a more normal facial appearance had milder short stature [14]. However, dysmorphic features are heterogeneous, even amongst those with the same *GHR* mutations. As shown in figure 2b, 14 patients from Ecuador, age 1 month to 66 years, all homozygous for a splicing defect in exon 6 of the *GHR* gene (reported as E180sp), demonstrate heterogeneity in craniofacial abnormalities and phenotype, despite genetic homogeneity [15].

The human GHR protein can be divided into 3 segments (fig. 2a): a 245-amino acid extracellular domain; a short (24-amino acid residues) transmembrane domain (TM), and an intracellular domain (350 residues). GHR functions as a homodimer, with the dimeric extracellular domain involved in asymmetric binding of GH, and, in humans, this domain can also be proteolytically cleaved to circulate in serum as a GH-binding protein (GHBP). A reduction in serum GHBP often is indicative of a defect in GHR. Not surprisingly, ~90% of *GHR* mutations identified to date localize to this domain [10]. In contrast, only a handful of mutations have been identified in the GHR intracellular domain and none in the TM, although four splicing variants that lead to loss of the entire TM and supraphysiological levels of serum GHBP have been reported [16] (fig. 2a). The proportion of *GHR* mutations skewed towards the extracellular domain suggests ascertainment bias for analyzing the *GHR* gene only from patients with low GHBP, but recent studies suggested that it requires the loss of all critical regions within the intracellular domain for an intracellular mutation to be clinically significant [13, 17]. Interestingly, all three *GHR* dominant-negative mutations are located in the intracellular domain, while all 60 mutations in the GHR extracellular domain are recessive.

The impact of *GHR* mutations on height phenotype and IGF-I production is diverse, and lacks distinct phenotype-genotype correlations. Of the
Fig. 2. Mutations in the human GHR gene. a Schematic of the GHR protein and gene, type of mutations identified, and predominant clinical biochemistries. b Heterogeneity in craniofacial features in an Ecuadorian cohort with same homozygous, in-frame, splicing GHR mutation (published as E180sp). From Rosenfeld et al. [15].
spectrum of mutations identified in GHR (fig. 2a), an unexpected relationship between the type mutation and height SDS was recently revealed, with nonsense and missense mutations conferring the severest impact on growth phenotype [10] (fig. 2c). Height SDS became progressively less severe with mutations involving splicing events (two of the dominant mutations are also splicing mutations), reflecting the probability of splicing inefficiency leading to presence of a small proportion of normal GHR. Indeed, this was demonstrated in unrelated patients carrying the same ‘pseudoexon’ mutation, a splicing mutation (c.618+792A>G, intron 6) that resulted in an in-frame insertion of 36 amino acid residues [18]. The type of mutations, furthermore, also influenced IGF-I production (fig. 2c).

It is apparent that effects on IGF-I production and subsequent growth phenotype depends less on location of the GHR mutation and more on the severity of disruption to GHR expression and function. Demonstrations of the functional impact of identified GHR mutations are, therefore, critical to understanding clinical presentations.

**Mutations in the STAT5B Gene: STAT5b Signaling Mediates GH-Induced IGF-I Production**

The recent identification of severe growth failure and marked IGF deficiency associated with mutations of the STAT5B gene (17q11.2; OMIM #245590) [19, 20] was the first demonstration that, in humans, the STAT5b signaling pathway, of all pathways activated by the GH-GHR-JAK2 system, is critical
for both IGF-I production and normal growth. This, together with identified GHR mutations associated with isolated failure of STAT5b signaling [21, 22] strongly supports the hypothesis that GH-induced regulation of IGF-I production is mediated predominantly through activation of the STAT5b signaling pathway (fig. 1).

Seven unique STAT5B mutations have now been identified in 10 described STAT5b-deficient patients (7 females, 3 males), including 2 sets of siblings [20]. In humans, size at birth of affected individuals, when available, has been normal or slightly reduced, similar to the characteristics of children with congenital GH deficiency or defects of the GHR, and consistent with the fact that IGF production in utero is largely GH independent. Postnatal growth has been uniformly poor, with deceleration evident within the first year of life. Heights have ranged from −4.9 to −9.9 SD, again similar to observations in defects of the GHR. Mild facial dysmorphic features, such as a prominent forehead, depressed nasal bridge and high-pitched voice, were noted for some of the STAT5b-deficient subjects. Serum concentrations of IGF-I, IGFBP-3 and ALS have been strikingly reduced and basal and stimulated GH concentrations have been either normal or increased. Administration of GH has resulted in little increase in serum IGF-I concentrations and no acceleration of linear growth. Altogether, growth patterns and serum concentrations of GH, IGF-I, IGFBP-3 and ALS have been indistinguishable from those observed in patients with severe defects of the GHR. As in the overwhelming majority of cases with severe defects of the GHR, the transmission of STAT5B mutations appears to be autosomal recessive.

The one distinguishing feature of patients carrying STAT5B mutations that was absent in patients with GHR or IGF1 mutations was the histories of immune dysregulation [23]. Severe eczema from a very young age was reported in all STAT5b-deficient cases, and all but one of the cases presented abnormal immunological profiles and/or symptoms of chronic pulmonary disease due to inflammation. Indeed, 2 of the patients succumbed and died as a consequence of progressive pulmonary fibrosis and respiratory failure [20], and one underwent a successful lung transplantation at age 17.5 years that appeared to have alleviated impaired pulmonary functions [24]. This complex phenotype correlates with the importance of STAT5b signaling pathway in multiple cytokine systems involved in immunity.

**IGFALS Mutations: Mild Short Stature Despite Severe Deficits in Circulating IGF-I**
Approximately 80–85% of circulating IGF-I is found in complex with IGFBP-3 (and, to a lesser extent, IGFBP-5) and ALS. ALS, encoded by the 3.3-kb IGFALS gene (consisting of 2 exons; 16p13.3; OMIM 601488), is an 85-kDa glycoprotein that is produced almost exclusively by the liver and secreted into the circulation. It is highly structured, with 20 leucine-rich repeat motifs that participate
in protein-protein interactions, arranged in a donut-like shape [25]. The main function of ALS appears to be prolonging the half-life of the IGF-I-IGFBP-3 binary complexes, which interact with patches of electronegative regions within the center of the ALS cavity. The identification of the first case of an inactivating mutation in the human IGFALS gene, associated with short stature, insensitivity to GH and abnormally low serum IGF-I and IGFBP-3 levels, provided direct support for the importance of ALS in the maintenance of normal serum IGF-I and IGFBP-3 levels [26].

Since the first report of complete ALS deficiency in 2004 [26], a total of 21 cases (children and adolescents) have been characterized at the molecular level [27]. Auxological and biochemical analysis indicated that complete ALS deficiency was consistently characterized by: (a) a severe reduction in serum IGF-I and IGFBP-3 concentrations that are incongruent with the mild postnatal growth retardation (height SDS –2 to –3 SDS before and during puberty); (b) an insulin insensitivity characterized by normal glucose and increased insulin levels; (c) a pubertal delay that was found in about half of the male subjects, and (d) a poor response to GH treatment, both in terms of growth acceleration and increase in IGF-I and IGFBP-3 levels.

Sixteen different IGFALS mutations, all autosomal recessive, were identified in the 21 patients studied [27]. Twelve patients were found to be homozygous and 9 were compound heterozygous, with approximately one third of the patients (8 patients from 3 families) being familial cases. All the mutations were located in exon 2 (exon 1 encoding only 5 amino acids), with the majority found in one of the 20 leucine-rich repeat regions, and resulted in either a complete absence, or barely detectable, ALS levels. The lack of ALS totally disrupted the entire circulating IGF system. In contrast, peripheral production of IGF-I presumably remained unaffected, as stability of peripheral IGF-I depends only on IGFBPs. Hence, peripheral production of IGF-I and perhaps a rapid efflux of circulating IGF-I to the extravascular compartments may explain why the magnitude of postnatal growth retardation in ALS-deficient patients is less pronounced than might be predicted from the apparent severe deficit in circulating IGF-I. How ALS deficiency leads to insulin resistance, remains poorly understood.

IGF1R Mutations: A Molecular Cause of IGF-I Resistance and Intrauterine Growth Retardation

A key feature of IGF1R defects (15q26.3; OMIM*147370) is the association with impaired fetal growth, not observed with other genetic causes of GHI, with the exception of IGF1 mutations. Patients carrying IGF1R defects display a more variable degree of intrauterine and postnatal growth retardation (height SDS –2 to –4.9), compared to patients carrying homozygous IGF1 mutations, and often, but not invariably, accompanied by microcephaly, dysmorphic facies, and intellectual impairment [28]. Affected children fail to thrive despite normal or elevated serum IGF-I concentrations, and while GH therapy appropriately
increased serum IGF-I and IGFBP-3 levels, growth response has been uniformly poor. Interestingly, moderate insulin resistance (impaired glucose tolerance, elevated HOMA-IR values) has been associated with 2 reported cases [29, 30], and a recently identified IGF1R-deficient case (novel compound heterozygous mutations) presented with adolescent onset, insulin-dependent, diabetes [Cowell, pers. commun.].

Only heterozygous mutations (8 reported), and one patient with compound heterozygous mutations, in the IGF1R gene have been described to date [10, 28, 30]. Familial short stature associated with the heterozygous IGF1R mutations and the lack of consanguinity support in vitro demonstrations that dominant-negative effects and/or haploinsufficiency are causes of the observed pathophysiology.

**GH-IGF-I Axis: Defects in Other Signaling Pathways – Effects on IGF-I Production?**

Only a handful of mutations in the intracellular GH signaling components have been demonstrated to be convincingly associated with IGFD and growth retardation (see above). Of the other components, heterozygous mutations in the PTPN11 gene (encoding tyrosine phosphatase SH2 domain phosphatase-2), which acts as a negative regulator of GH-GHR signaling, are associated with Noonan syndrome, and result in mild GHI and IGFD [31, 32]. Somatic mutations in JAK2 have been identified in humans, but are limited to myoproliferative disorders [33–36]. Heterozygous mutations in components of the MAPK signaling pathways have been reportedly associated with Noonan, Costello and cardio-facio-cutaneous syndromes [37–42]; effects on IGF-I production are unknown. Altogether, clinical consequences of defects in these pathways do not necessarily reflect direct actions of GH or modulation of IGF-I productions.

**Conclusions**

The fundamental importance of the human GH-IGF axis is the production of IGF-I so critical for human linear growth. A summary of phenotypic and biochemical features of key defects is shown in table 1 [10], all of which result in growth impairment leading to childhood and adult short stature. Defects in the GHR, STAT5B, and IGF1 genes have the severest consequences, with demonstrated IGFD and GHI. Mutations in the IGF1 gene, in addition, affect in utero growth, as do IGF1R mutations. Other clinical consequences noted, including immune deficiencies associated with STAT5B mutations and mild insulin resistance with IGFALS mutations.

Therapies designed to correct growth are limited at present. The resistance to GH therapy suggest that recombinant human IGF-I treatment, now approved
by the US Food and Drug Administration for children with height SD score of –3 or less, serum IGF-I score of –3 or less (<2.5th percentile in the EU), and normal or elevated GH, could be a therapeutic option, except for patients who are IGF-I resistant.

An algorithm showing key steps in the investigation of genetic defects in the GH-IGF-I axis is indicated in figure 3 [10]. Even with advances in molecular endocrinology related to growth disorders, it becomes apparent that detailed phenotypic evaluation and documentation is of crucial importance. Evaluation of a child with short stature and possible GHI should, therefore, comply with the classical paradigm of detailed clinical and endocrine assessments prior to consideration for genetic analyses. Finally, despite our increased knowledge of the role of IGF-I in linear growth, the precise etiology in many children with short stature remains unclear. Continued investigation of patients with abnormal growth will, ultimately, facilitate better diagnosis and improve management of children presenting with abnormal growth and development.

### Table 1. Summary of phenotypic and biochemical features of key defects in the GH-IGF-I axis

<table>
<thead>
<tr>
<th>Gene defect/phenotype</th>
<th>GHR</th>
<th>STAT5B</th>
<th>IGF1</th>
<th>IGFALS</th>
<th>IGF1R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe growth failure</td>
<td>+/−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Mild growth failure</td>
<td>−/+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mid-face hypoplasia</td>
<td>+/-</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Other facial dysmorphism</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+/−</td>
</tr>
<tr>
<td>Deafness</td>
<td>−</td>
<td>−</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Intellectual delay</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+/−</td>
</tr>
<tr>
<td>Puberty delay</td>
<td>+/-</td>
<td>+/−</td>
<td>−</td>
<td>+/−</td>
<td>−</td>
</tr>
<tr>
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<td>−</td>
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<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Hypoglycemia</td>
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<td>−/+</td>
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<tr>
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<td>+/−</td>
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<td>IGF-I deficiency</td>
<td>+</td>
<td>+</td>
<td>+/−</td>
<td>+</td>
<td>−</td>
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<tr>
<td>IGF-I resistance</td>
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<td>−/+</td>
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<td>+</td>
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<tr>
<td>IGFBP-3 deficiency</td>
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<td>ALS deficiency</td>
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<tr>
<td>GH excess</td>
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<td>Homozygous mutations</td>
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<td>Heterozygous mutations</td>
<td>−</td>
<td>−</td>
<td>−/+</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

From David et al. [10] with modifications. + = Consistently observed; − = not observed; +/- = predominantly observed; −/+ = sometimes observed.
Fig. 3. Algorithm showing key steps in the investigation of genetic defects in the GH-IGF-I axis. From David et al. [10].

References


Non-Imprinted Epigenetics in Fetal and Postnatal Development and Growth

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\textbf{Abstract}

Recent evidence demonstrates that the environment in early life can have important effects on fetal and postnatal growth, on development and on risk of developing common non-communicable diseases in later life. In animals, the environment during early life induces altered phenotypes in ways which are influenced or mediated by epigenetic mechanisms. The latter include DNA methylation, covalent modifications of histones and non-coding RNAs. Most is known about DNA methylation changes, which are gene specific, include effects on non-imprinted genes and function at the level of individual CpG dinucleotides to alter gene expression. Preliminary evidence from human studies suggests a similar important role for epigenetic processes. Tuning of phenotype by the developmental environment has adaptive value because it attempts to match an individual’s responses to the environment predicted to be experienced later; hence, such processes have been selected during evolution as conferring fitness advantage. When the phenotype is mismatched, e.g. from inaccurate nutritional cues from the mother or placenta before birth, or from rapid environmental change through improved socioeconomic conditions, risk of non-communicable diseases increases. Evidence is accruing that endocrine or nutritional interventions during early postnatal life can reverse epigenetic and phenotypic changes induced, for example, by unbalanced maternal diet during pregnancy. Elucidation of epigenetic processes may enable early intervention strategies to improve early development and growth.

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Fixed genomic variations explain only a fraction of the variability in the development, growth and later metabolic disease risk of human infants [1, 2]. However, there is increasing evidence suggesting an important role for perinatal environmental factors [3, 4]. For example, famine during pregnancy is associated with fetal and postnatal growth and with the risk of obesity in the adult offspring [5], and normal variations in maternal body composition relate to child’s later adiposity [6]. This adds to research worldwide which has established that people who were small at birth and had poor growth in infancy have increased rates of coronary heart disease, raised blood pressure and impaired glucose tolerance, particularly if their restricted fetal and infant growth was followed by increased childhood weight gain. There is now evidence that both premature birth and fetal growth restriction are associated with adverse long-term effects. The relations between smaller infant size and an increased risk of ill-health and adult disease extend across the normal range of infant size in a graded manner and cannot be explained by confounding variables acting during adult life.

The observations have led to the hypothesis that coronary heart disease, hypertension and type 2 diabetes originate through developmental plastic responses made by the fetus and infant as part of a prediction of the subsequent environment to which it anticipates that it will be exposed. Exposures during critical periods in development can have long-term consequences; if the environment in childhood and adult life differs from that predicted during fetal life and infancy, the developmental responses may increase the risk of adult disease. In those human societies where economic circumstances and nutrition are rapidly improving, a mismatch between the early prediction and the subsequent reality can cause severe health problems.

Evolutionary considerations and experimental findings in animals strongly support the existence of major environmental effects on early growth and later life metabolic function. Variations in growth, development and later cardiovascular and metabolic physiology can be induced experimentally by manipulation of the developmental environment, for example by altering maternal nutrition or administering glucocorticoids during pregnancy, often without necessarily affecting the birth size of the offspring.

It is now clear that the associations between early development and later outcomes do not simply reflect genetic influences. Rather, the findings indicate that interactions between the genetic influences and the early life environment determine metabolic function, susceptibility to adverse environmental challenges and disease in later life. Such concepts are fundamental to current life course strategies to the prevention and treatment of non-communicable diseases (NCDs; fig. 1). NCDs do not fit the medical model in which an individual is healthy until they contract the disease. Risk increases throughout the life course as a result of declining plasticity and the resulting accumulative effects of inadequate responses to new challenges. However, although the greatest increase occurs in adult life, the trajectory is set much earlier, being influenced by factors such
as the mother’s diet and body composition before and during pregnancy, and fetal, infant and childhood nutrition and development. Adopting a life course perspective allows identification of phenotype and markers of risk early, with the possibility of nutritional and other lifestyle interventions. Timely, relatively modest interventions in early life (area in black) can have a large effect on disease risk later (black arrow), while later intervention (area in grey) can remain impactful for vulnerable groups (grey arrow). Early-life preventive measures require a long-term investment, but are more likely to be effective than population screening programs that identify the early stages of disease or treatments initiated after the disease is manifest.

While understanding of the mechanisms underlying long-term effects of the early life environment is limited, data from animal models suggest that epigenetic processes in non-imprinted genes are an important link between exposures such as maternal diet and both altered early development and later body composition in adulthood [7–9]. Moreover, there is now evidence that elements of the heritable or familial component of susceptibility to cardiovascular disease, obesity and other NCDs can be transmitted across generations by non-genomic means.

In animals, the developmental environment induces altered phenotypes through genetic, physiological (especially endocrine) and epigenetic mechanisms. The latter include DNA methylation, covalent modifications of histones and non-coding RNAs. We are only now starting to appreciate that subtle
epigenetic processes in non-imprinted genes, perhaps affecting only a subset or clone of cells, also have major roles in human and animal development. Such ‘tuning’ of phenotype has potential adaptive value and may confer Darwinian fitness advantage because it either adjusts the phenotype to current circumstances and/or attempts to match an individual’s responses to the environment predicted to be experienced later. When the phenotype is mismatched to the later environment, e.g. from inaccurate nutritional cues from the mother or placenta before birth, or from rapid environmental change through improved socioeconomic conditions, risk of NCDs increases. Such mechanisms are also thought to play roles in ageing and early onset of puberty, reinforcing a life course perspective on such adaptive responses, especially the detrimental later effects of trade-offs.

Regulated DNA methylation changes induced during development are gene specific and function at the level of individual cytosine nucleotides immediately 5’ to a guanine (CpG sites) in both gene promoter and intergenic regions. Evidence is accruing that endocrine or nutritional interventions during early postnatal life can reverse epigenetic and phenotypic changes induced, for example, by unbalanced maternal diet during pregnancy. Elucidation of epigenetic processes may permit perinatal identification of individuals most at risk of later NCDs and enable early intervention strategies to reduce such risk.

Epigenetic processes such as DNA methylation and histone modifications allow the developmental environment to modulate gene transcription; many of these changes are then stable throughout the life course [10, 11]. Such processes are involved not only in cell differentiation and parental genomic imprinting but also in developmental plasticity through which the environment in early life can affect the developmental trajectory, with long-term effects on gene expression and on phenotypic outcome [12–14]. For example, in the rat unbalanced maternal diet during pregnancy induces changes in DNA methylation and covalent histone modifications in the 5’ regulatory regions of specific non-imprinted genes [15–17] and affects the offspring’s later body composition and metabolic phenotype. Induced changes in phenotype can be prevented by nutritional interventions during pregnancy [18], or altered by nutritional interventions during the juvenile-pubescent period [19] or by hormonal interventions during suckling [20].

While epigenetic processes operating in early development have been implicated in perinatal growth and later body composition [3, 11], until recently there has been little direct evidence for this proposition in humans. Using Sequenom MassARRAY, we measured the methylation status of 68 CpGs 5’ from five candidate non-imprinted genes in umbilical cord tissue DNA from healthy neonates [21]. Methylation varied greatly at particular CpGs. For 31 CpGs with median methylation ≥5% and a 5–95% range ≥10%, we related methylation status to maternal pregnancy diet and to child’s adiposity at age 9 years; 7 had significant associations with child’s adiposity age 9 years. Further analyses found
that greater methylation of a single CpG within the RXRA promoter measured in umbilical cord was robustly associated with greater adiposity in later childhood [21]. The associations reflect clinically important shifts in adiposity such that the mean fat mass rose from 4.8 kg (17.3% body fat) in the lowest quarter of RXRA methylation to 6.6 kg (21.3% body fat) in the highest quarter of the distribution. Regression analyses including sex and neonatal epigenetic marks explained >25% of the variance in childhood adiposity. These findings were replicated in a second independent cohort (fig. 2).

Given the complexities of retinoid receptor biology, increased RXRA methylation might be acting through a variety of pathways, but an association between increased RXRA methylation and adiposity is consistent with the observation of strongly diminished RXRA expression in visceral white adipose tissue from obese mice [22]. Moreover, a role for retinoid receptor methylation in developmental influences on later adiposity is supported by recent experimental data showing an influence of maternal diet during pregnancy on methylation of LXRA, a heterodimeric partner of RXRA [23]. Although epigenetic changes can be dynamic, experimental studies have shown that environmental factors acting on the genotype during development relate to epigenetic profile in adulthood and there are longitudinal human studies showing that DNA methylation is often stable over time. Such changes can be tissue specific, and in this respect

![Graph showing the association between umbilical cord RXRA amplicon1 CpG13 methylation and child's percentage fat mass](image)

**Fig. 2.** In two independent cohorts, a DNA methylation ‘mark’ in umbilical cord induced by the environment in utero predicts child’s later adiposity. Values are expressed as means + SEM.
the umbilical cord may be advantageous because it contains a high proportion of fetal vascular tissue and mesenchymal cells which may be relevant to later adiposity. While experimental work in the rat suggests that methylation changes induced by maternal diet can be similar in the umbilical cord and liver [24], further work is needed to determine the relevance of epigenetic changes in human umbilical cord tissue. Recent data show that for some genomic regions methylation appears largely independent of tissue of origin, while for others there is a clear tissue-specific dependence [25].

In the above human studies, associations were also observed between levels of RXRA methylation and the mothers’ carbohydrate intake, supportive of the concept that nutritional conditions in early pregnancy can affect a child’s adiposity in later life [21]. The work provides novel evidence of a role for epigenetic changes in non-imprinted genes in relation to early development and suggests that specific components of the epigenetic state at birth might be used to predict adiposity in later childhood.

During development, environmental variations within the normal range change expression of non-imprinted genes, resulting in altered growth and metabolic phenotypes that have implications for later health and disease. Taken together, the animal and human studies support the notion that epigenetic processes in non-imprinted genes are able to exert a fine control on developmental outcomes. Epigenetic changes, in particular DNA methylation, provide a ‘memory’ of developmental plastic responses to early environment and are central to the generation of phenotypes and their stability through the life course. Understanding these processes may lead to novel insights into evolutionary biology and the risk of disease.

References


Epigenetic Anomalies in Childhood Growth Disorders

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Abstract

Fetal growth is a complex process involving environmental, epigenetic and genetic factors. Fetal growth restriction is associated with morbidity among small for gestational age (SGA) neonates as well as in children and adults who were former SGA. Imprinted genes (whose expression is restricted to a single parental allele) have a critical role in controlling mammalian fetal growth. The human chromosome 11p15 encompasses two imprinted domains regulated by their own differentially methylated imprinted control region (ICR1 at the \(H19/IGF2\) domain, and ICR2 at the \(KCNQ1/CDKN1C\) domain). Loss of imprinting at these two domains is implicated in two clinically opposite growth disorders. Indeed, our group has identified a loss of DNA methylation (LOM) at ICR1 in over 50% of patients with Russell-Silver syndrome (RSS) characterized by intrauterine and postnatal growth retardation with spared cranial growth, dysmorphic features, frequent body asymmetry and severe feeding difficulties. By contrast, gain of methylation at ICR1 is found in 10% of patients with Beckwith-Wiedemann syndrome (BWS), an overgrowth syndrome with an enhanced childhood tumor risk. We have now identified over 130 RSS patients with 11p15 LOM. This 11p15 epimutation is a frequent and specific cause of RSS as it has not been identified in non syndromic SGA patients. These new findings in the pathophysiology of RSS allow long-term follow-up studies to be performed based on molecular diagnosis. This will help to define appropriate clinical guidelines regarding growth, rapid bone age advance during puberty and feeding difficulties. Remarkably, we have also recently found that ~10% of RSS patients and ~25% of BWS patients showed multilocus LOM at imprinted regions other than ICR1 or ICR2 11p15, respectively. Several clinical studies demonstrated that assisted reproductive technology significantly increased the risk of human imprinting diseases including BWS and RSS, suggesting that the environment may favor imprinting disorders.
**Introduction**

Fetal growth is a complex process involving multiple environmental, epigenetic and genetic factors. Intrauterine growth retardation or small for gestational age (IUGR/SGA) represents about 5% of the births, and is associated with severe morbidity. Indeed, IUGR patients are exposed to an enhanced risk to develop cardiovascular or metabolic diseases in adult life (fetal programming or the adaptation hypothesis, developmental origins of health and disease) [1]. By contrast, fetal overgrowth syndromes are associated with developmental abnormalities, tissue and organ hyperplasia and a higher risk of childhood tumors [2]. It has been recognized that faithful genetic and epigenetic programming has a critical role in controlling mammalian fetal and postnatal growth. The most studied epigenetic mark is DNA methylation of CpG dinucleotide cytosine residues within gene promoters, transposons and imprinted regions. Genomic imprinting is an epigenetic mechanism whereby expression of a subset of genes is restricted to a single parental allele. The majority of imprinted genes are organized in clusters throughout the genome and are regulated by an imprinting control region (ICR) [3]. The methylation of the genome undergoes dynamic reprogramming during fetal development. The first step takes place in primordial germ cells where methylation is erased from the ICRs and further reestablished, on cytosine residues of the CpG dinucleotides, according to the gender-specific gamete [4]. The second important widespread epigenetic reprogramming occurs in the preimplantation period, where the whole genome undergoes a wave of general demethylation soon after fertilization, while the imprinting is maintained during this period and then followed by a progressive wave of lineage-specific de novo methylation beginning at the blastocyst stage. The mechanisms leading to the establishment and maintenance of allele-specific DNA methylation at ICRs throughout fetal development and adulthood are very complex and not fully understood. They involve not only cis- and transacting regulatory factors [5, 6], but also influenced by environmental conditions such as dietary factors or assisted reproductive technology (ART) [7–9]. Loss of imprinting (LOI) through gain (GOM) or loss (LOM) of DNA methylation is implicated in several human diseases and cancer [8]. The human chromosome 11p15 encompasses two imprinted domains (fig. 1) important in the control of fetal and postnatal growth. Each domain is differentially methylated and regulated by its own ICR (ICR1 at the telomeric region for the H19/IGF2 domain which is methylated on the paternal allele, and ICR2 at the centromeric region for the KCNQ1OT1/CDKN1C domain which is methylated on the maternal allele). LOI at these two domains is involved in two clinically opposite growth disorders. Indeed, LOM at ICR1 is identified in over 50% of Russell-Silver syndrome (RSS; a growth restriction syndrome) patients [11, 12], whereas GOM at ICR1 is found in 10% of Beckwith-Wiedemann syndrome (BWS; an overgrowth syndrome with an increased tumor risk).
patients with identified molecular anomalies [13]. The great majority of BWS cases are associated with other molecular defects within the 11p15 region (see above), but this clinical and molecular mirror demonstrates the crucial role of the imprinted IGF2 gene in fetal growth. Several other human diseases are explained by deregulation of imprinted gene expression, but epimutations are less frequent than in RSS and BWS (table 1).

Fig. 1. Normal 11p15 epigenetic organization and molecular defects in RSS and BWS. The telomeric ICR1 domain regulates the expression of IGF2 and H19 during fetal life. IGF2 is expressed exclusively from the methylated paternal allele (P), and H19 is expressed exclusively from the unmethylated maternal allele (M). The maternally methylated centromeric ICR2 regulates the expression of CDKN1C (maternal expression) and KCNQ1OT1 (paternal expression). Expressed genes are represented by white boxes and non-expressed genes by gray boxes. In RSS patients, ICR1 LOM leads to loss of IGF2 expression and H19 biallelic expression. In BWS patients, ICR1 GOM leads to loss of H19 expression and IGF2 biallelic expression; ICR2 LOM leads to loss of CDKN1C expression and KCNQ1OT1 biallelic expression; pUPD leads to IGF2 overexpression. Maternal CDKN1C mutations also lead to BWS.
**Clinical Diagnosis**

Russell-Silver Syndrome (RSS) is a clinically heterogeneous syndrome characterized by severe intrauterine growth restriction (IUGR) with relative macrocephaly, postnatal growth retardation, a distinctive triangular face with prominent forehead and body asymmetry [14–16]. Many other minor signs have been added including clinodactyly of the fifth finger, café-au-lait spots, genital abnormalities, hypoglycemia, excessive sweating, blue sclera and severe feeding difficulties. No consensus definition has yet been adopted. Recent findings in the molecular diagnosis of the syndrome (see above) prompted several teams to propose more or less complex clinical scores to establish genotype/phenotype correlations [12, 17–20]. Based on a large cohort of >150 RSS patients [12 and unpubl. data] with an identified molecular defect, we proposed a validated clinical scoring system for the diagnosis of RSS:

- the patient must be born SGA (birthweight and/or length ≤–2 SDS for gestational age), and
- the patient must present at least 3 of the following 5 criteria: (1) postnatal growth retardation at 2 years of age or at the nearest measure available, (2) relative macrocephaly (i.e. arbitrarily defined when the head circumference at birth is at least 1.5 SDS above the birthweight and/or length), (3) body asymmetry.

### Table 1. Frequency of epimutation in different imprinting disorders

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>OMIM</th>
<th>Growth phenotype</th>
<th>Frequency of epimutation, %</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient neonatal diabetes mellitus</td>
<td>601410</td>
<td>IUGR</td>
<td>20</td>
<td>6q24</td>
</tr>
<tr>
<td>RSS</td>
<td>180860</td>
<td>IUGR, short final height</td>
<td>0</td>
<td>mUPD11p15</td>
</tr>
<tr>
<td>BWS</td>
<td>130650</td>
<td>macrosomia</td>
<td>60</td>
<td>11p15</td>
</tr>
<tr>
<td>mUPD14-like syndrome</td>
<td></td>
<td>IUGR, overweight, precocious puberty, short final height</td>
<td>?</td>
<td>14q32</td>
</tr>
<tr>
<td>Angelman syndrome</td>
<td>105830</td>
<td>&lt;5</td>
<td></td>
<td>15q11-13</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td>176270</td>
<td>severely overweight, short final height</td>
<td>1–2</td>
<td>15q11-13</td>
</tr>
<tr>
<td>Pseudohypoparathyroidism 1a/1b</td>
<td>103580</td>
<td>short final height</td>
<td>?</td>
<td>20q13</td>
</tr>
</tbody>
</table>
asymmetry, (4) prominent forehead and (5) feeding difficulties during early childhood and/or postnatal body mass index (BMI) below –2 SDS at 2 years of age or at the nearest measure available.

Of note, we have included feeding difficulties and/or low BMI as one of the criteria as they are reported to be particularly frequent and severe in RSS during infancy and early childhood. This manifestation can be associated with frequent gastrointestinal disorders, such as constipation, gut dysmobility, gastroesophageal reflux disease [21]. We have retained the prominent forehead as the main characteristic of facial dysmorphism, but it should be assessed before 3 years of age since the characteristic facial features of the RSS seem to change, and are not as marked in late childhood and adulthood [12, 19].

Molecular Diagnosis

The genetic cause of RSS was unknown for a long time. Most of the cases are sporadic, both genders are equally affected. The first molecular abnormality identified in a significant proportion of patients was maternal uniparental disomies (mUPD) for chromosome 7 (mUPD7), present in around 7–10% of the cases [22]. mUPD7 involves either iso- or heterodisomy of the whole chromosome in most subjects. This finding implies that one or more genes on this chromosome are imprinted, and that disturbed imprinting is responsible for the phenotype. So far, two candidate regions on chromosome 7 have been the focus of research: 7p11.1-p14 and 7q31, for which a number of RSS patients with duplications (or inversions) or segmental UPD have been reported. These regions harbor imprinted genes possibly involved in human growth and development like GRB10 and PEG1/MEST. However, their implication in the physiopathology of the syndrome has not been demonstrated yet.

In 2005, our group described the main molecular defect associated with RSS: ICR1 LOM, present in more than 50% of the cases [11, 12]. In most of the cases, the LOM is partial, reflecting the mosaic distribution of the epimutation. In RSS patients, the paternal allele switches to a maternal epigenotype resulting in biallelic expression of H19 and loss of IGF2 expression in pathologic cells (fig. 1). The cause of this epimutation remains unknown. Mosaic distribution and LOM at multiple loci (see later) argue for a postzygotic occurrence of the epimutation.

Genotype/Phenotype Correlations

RSS patients with ICR1 LOM often display a more severe phenotype regarding growth parameter with a more typical dysmorphism (relative macrocephaly, prominent forehead) and body asymmetry [12, 19, 20].

Specific features of mUPD7 RSS patients are mild developmental delay mainly consisting in speech difficulties, predisposition to myoclonus dystonia and a putative susceptibility to develop autism traits [20, 23, 24]. All these features are thought to be related to disruption of expression of specific imprinted genes on chromosome 7.
Beckwith-Wiedemann Syndrome

Clinical Diagnosis
BWS is a rare overgrowth disorder involving developmental abnormalities, tissue and organ hyperplasia and an increased risk of childhood tumors [25]. It is generally accepted that diagnosis of BWS requires at least 3 clinical findings including at least 2 major signs which are macroglossia, macrosomia at birth or postnatal overgrowth, abdominal wall defect (ranging from umbilical hernia to exomphalos) and organomegaly. Minor findings include neonatal hypoglycemia, ear creases and pits, facial nevus, hemihyperplasia and embryonal tumors.

Molecular Defect
BWS results from molecular or chromosomal alterations that cause overexpression of the paternally expressed genes or a lack of expression of the maternally expressed genes within the 11p15 region [25, 26] (fig. 1):
- LOM at ICR2 (50–60% of cases)
- UPD of paternal origin (pUPD; 20% of cases)
- GOM at ICR1 (5–10%)
- Genic mutation on the maternal allele of the CDKN1C gene (5% of cases)
- Cytogenetic anomalies (1–2% of cases) consisting of maternally inherited balanced rearrangements (translocations or inversions) and trisomy with double dose of the paternal 11p15 region (resulting from duplications or unbalanced reciprocal translocation involving the 11p15 region)

All those molecular defects display a mosaic pattern except CDKN1C mutation and cytogenetic anomalies.

Genotype/Phenotype Correlations
Genetic diagnosis and molecular characterization are important to determine the outcome of BWS and perform reliable genetic counseling. Particularly, pUPD and GOM at ICR1 result in a high risk of nephroblastoma while CDKN1C mutations can be inherited and cause familial recurrence [25, 26]. CDKN1C mutations are strongly associated with exomphalos, whereas macrosomia is more frequent in ICR1 GOM [27 and unpubl. data].

Human Multilocus Imprinting Disorders
Imprinting disorders are complex syndromes and display a high degree of clinical heterogeneity. Until a few years ago, it was believed that LOI leading to various human syndromes were isolated events affecting only a given locus involved in a particular syndrome. However, we found that a subset of BWS patients, including some born after ART, displayed LOM at imprinted loci other than the ICR2 11p15 region [27]. Concomitantly, Mackay et al. [28] reported a subset of
transient neonatal diabetes mellitus patients with 6q24 LOM (ZAC1 DMR) also displaying multilocus imprinting defects. Since these two reports, other groups have described multilocus imprinting defects in BWS and in TNDM patients. More recently, we revealed that about 10% of RSS patients exhibit multilocus LOM at both paternally and maternally methylated loci, and that over two thirds of these patients exhibit LOM at DLK1/GTL2 IG-DMR 14q34 in addition to that at ICR1 11p15 [29]. These regions are two of the three paternally methylated ICRs. Comparisons between the clinical characteristics of monolocus LOM patients and multilocus LOM patients did not reveal any statistically significant differences. First idea was that the dominant phenotype is determined by the locus of more extensive demethylation. However, we observed that some RSS patients have similar degrees of LOM at different loci but only the RSS phenotype. This led us to suggest an epidominance effect exerted by the 11p15 region in the expression of the phenotype. However, imprinting disorders have complex phenotypes, and some of them share some clinical characteristics, for example TNDM and BWS (abdominal defects and macroglossia) and RSS and chromosome 14-related syndromes (IUGR). For these overlapping features, it is difficult to relate the observed clinical abnormality to one or another given locus. Most multilocus defects are partial, thus reflecting a degree of mosaicism. The expression of one syndrome rather than another may possibly therefore be explained by tissue-specific mosaicism.

**Assisted Reproductive Technologies and Loss of Imprinting**

Several studies reported the increased incidence of ARTs conception in BWS and Angelman syndrome patients [9, 30]. This finding seems also relevant for RSS patients with ICR1 LOM [19 and unpubl. data]. In mice, IVF and embryo culture lead to LOI of several genes including Igf2 and h19 [30]. To date, no specific procedure has been identified. It appears that the environment acts through epigenetic mechanisms to modulate development. Patients born after ART exhibiting an imprinting defect illustrate the link between early conception environment and epigenetic changes. Larger series are needed to investigate this further. Identification of the factors involved in the maintenance and/or the establishment of imprinting are undoubtedly crucial for understanding both the mechanisms underlying imprinting regulation and which disruptions lead to complex diseases such as RSS and BW.

**Conclusion**

The identification of ICR1 LOM and mUPD7 in nearly 70% of patients with RSS is a considerable step towards understanding the pathophysiology of this disorder. It involves imprinted genes like IGF2 and H19 within the 11p15 region. It
also involves imprinted genes on chromosome 7 that remain unidentified. In the same way, it is not established if there is an interaction between chromosome 7-encoded factors and the growth-relevant region 11p15. Long-term, systematic endocrine follow-up of cohorts of RSS patients with ICR1 LOM and mUPD7 will help to clarify phenotypic specificity and to draw appropriate guidelines for the clinical management. In 30% of patients with a clinical diagnosis of RSS, the underlying molecular defect is unknown. However, the relatively non-specific features of RSS present a continuing challenge to clinical diagnosis. This is why the use of a clinical score could help to reduce the heterogeneity of patients with idiopathic RSS. Identification of the factors involved in the maintenance and/or the establishment of imprinting is undoubtedly crucial for understanding both the mechanisms underlying imprinting regulation and which disruptions lead to complex diseases such as RSS and BWS.

References


Early Growth and Development of Later Life Metabolic Disorders

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Abstract

Growth is effected via a complex interaction of genetic, nutritional, environmental and growth factors. Hormonal factors such as the growth hormone (GH) and insulin-like growth factor (IGF) signaling system, the human placental lactogen, and insulin play an integral role in early growth. Genetic factors affecting the GH-IGF system and insulin secretion and actions, and epigenetic mechanisms including DNA methylation have been further implicated as contributory factors. These hormonal systems, on a background of genetic susceptibility, together with other factors including maternal nutrition, placental and environmental factors, regulate not only early growth but also development. These interactions may impact on later health consequences in adult life. Accumulating data in the last few decades on developmental programming and later life metabolic disorders has provided a novel perspective on the possible pathogenesis of metabolic dysregulation. Despite postulations put forward to elucidate the mechanism underlying the association between early growth and later life metabolic disorders, it remains unclear what the dominant factor(s) would be, how any underlying mechanisms interact, or whether these mechanisms are truly causal.

Introduction

Growth, as the preparation of the living being for adaptation, survival, and reproduction, calls upon a highly effective and integrated system of interacting growth factors and hormones. Reports of rare individuals with genetic defects and various animal studies have allowed us to gain a deeper understanding of the roles of many of the genetic factors, hormones and growth factors involved
in growth and development. Recent epidemiological observations have revealed an association between early growth and the development of metabolic disorders in later life, raising many hypotheses on early-life programming and developmental plasticity.

We review the physiology of growth, the phenomenon of developmental programming of later life metabolic disorders and provide an overview of the possible mechanisms underlying such programming.

**Physiology of Growth**

Growth requires a complex interaction of various genetic, nutritional, environmental and growth factors and hormones in a highly regulated and timely fashion. It is now clear that the growth hormone (GH) and insulin-like growth factor (IGF) signaling system plays an integral role in both pre- and postnatal growth [1]. GH, which is synthesized in the anterior pituitary, is the main regulator of IGF, through which it exerts in part its growth-promoting action. IGF is in turn regulated by six IGF-binding proteins (IGFBPs), namely IGFBP-1 to IGFBP-6. IGFBPs are themselves regulated by IGFBP proteases that cleave the IGFBPs to low-affinity fragments, and have important roles to play in modulating the effects of IGFs and IGFBP [2]. The regulation of growth and cellular proliferation is dependent on the ultimate interactions between IGFs and the IGF receptors.

In the fetus, GH is produced by the anterior pituitary gland from the end of the 1st trimester of gestation, and circulating levels of GH reach relatively high levels as the gestation progresses [3]. Although studies with anencephalic fetuses suggested that GH was not primarily involved in human fetal growth [4], the identification of GH receptor (GHR) expressions in the fetus suggests a possible role of GH on fetal growth [5]. This is supported by observations that Laron dwarfs with inactivating GHR mutations are born 2 standard deviations (SDs) shorter than normal, and congenitally GH-deficient newborn babies have reduced birth length at birth [6]. Infants with congenital hypopituitarism are also observed to have birth lengths 0.8–1.7 SD below the mean [7], highlighting a contributory role of GH in prenatal growth. Despite these observations, the predominant regulator of fetal growth is mostly attributed to the IGF system. IGF production is largely independent of GH in the fetus. In the second trimester, both IGF-I and IGF-II are expressed in all human tissues with IGF-I continuously rising in the third trimester and beyond [8]. Knockout mice with either IGF-I or IGF-II deletion have severe growth retardation in utero with birthweight of only 60% of normal [9]. Mice with both IGF-I and IGF-II gene deletion simultaneously attain birthweight of only 30%, suggesting an additive role of both hormones in prenatal growth [10]. A case report of a human with IGF-I gene deletion exhibiting a pattern of growth parallel to
knockout mice suggested a similar role of the IGF system in prenatal growth in humans [11].

Besides the GH-IGF system, human placental lactogen, a protein hormone produced by the trophoblast cells of the placenta, shares structural homology with the GH, and has been shown to be involved in fetal metabolism and the growth and development of the placenta and the fetus [12]. Human placental lactogen promotes early embryonic growth and exerts its influence on the fetus by stimulating production of other hormones such as IGF-I and insulin [13].

Fetal insulin also plays a key role in the regulation of fetal growth and metabolism. Venous cord blood concentrations of insulin have been demonstrated to be significantly lower in small for gestational age neonates, and correlated with birth and placental weight and neonatal height [14]. In contrast, high fetal insulin in response to maternal hyperglycemia is responsible for the increased growth and macrosomia observed in infants born to mothers with gestational diabetes, demonstrating the integral role of insulin in fetal growth and development.

These hormonal interactions, together with multiple factors including maternal nutrition and health, placental and environmental factors on the backdrop of genetic susceptibility regulate growth and development of the fetus. Importantly, these interactions may herald an impact on the long-term health consequences in future adult life.

**Epidemiological Evidence of Early-Life Developmental Programming**

Barker et al. [15] observed more than 20 years ago that an association exists between the development of ischemic heart disease in adult life and men with low birthweights. Hales et al. [16] described that reduced growth in early life is strongly associated with impaired glucose tolerance and development of type 2 diabetes. Together, Hales and Barker described the ‘thrifty phenotype hypothesis’ which proposed that the epidemiological associations between poor fetal and infant growth and the subsequent development of type 2 diabetes and the metabolic syndrome result from the effects of poor nutrition in early life, which produces permanent changes in glucose-insulin metabolism [17]. The Dutch Famine Study described that the offspring of mothers exposed to the famine of 1944–1945 had an increased risk of later life glucose intolerance, coronary heart disease, a more atherogenic lipid profile, disturbed blood coagulation, increased stress responsiveness and more obesity [18]. Over the years, data have consistently proved the reproducibility of these epidemiological findings in various populations and ethnic groups. Studies of monozygotic twins where the diabetic twin had a lower birthweight further lend support that the environment plays a central role in mediating these associations [19]. Besides perinatal in-utero factors, epidemiological studies have indicated that postnatal factors in the form
of accelerated weight gain in early life also convey an increased risk of developing metabolic disorders in later life [20]. Although the association between the developmental plasticity of early life and the acquisition of metabolic diseases in adult life is well accepted, the underlying mechanisms affecting such an association remain unclear.

**Genetic Factors Modulating Growth and Metabolic Disorder**

Barker’s thrifty phenotype hypothesis places emphasis on the impact of environmental influence in the form of in utero nutrition on long-term programming of metabolic disorders. However, Hattersley and Tooke [21] proposed in 1999 in their fetal insulin hypothesis that this programming might be principally genetically determined. The basis for the fetal insulin hypothesis stems from the basis that genetic susceptibility is important for both birthweight and diabetes, and genes that reduce insulin secretion or increase insulin resistance will predispose to small babies as well as diabetes. In this hypothesis, insulin secretion and action are the main actor and the common pathway for the influence of genes. Insulin resistance and impaired insulin secretion are the common features of type 2 diabetes, and at the same time fetal insulin secretion is the main modulator of fetal growth in utero. This proposed genetically determined programming of the disorders of insulin secretion and action and the simultaneous effect on fetal growth have been supported in various single-gene disorders described in the literature. Glucokinase gene mutation, which causes mild β-cell dysfunction, can manifest as mild hyperglycemia. A mutation in the glucokinase gene in the mother resulted in a 601 grams increase in fetal size mediated through increased fetal insulin secretion in response to maternal hyperglycemia, but the same mutation in the fetus resulted in a 533 grams decrease in fetal size by decreasing fetal insulin secretion. When both mother and fetus had the glucokinase mutation, the two opposing effects cancelled out and the baby was of normal weight [22]. Other genes implicated in insulin secretion and fetal growth include the insulin promoter factor-1 gene. Homozygous mutation of this gene results in agenesis of the pancreas with markedly reduced fetal size to less than the 1st centile [23]. Homozygous mutations of the Kir6.2 and sulfonylurea genes result in persistent hyperinsulinemic hypoglycemia of infancy and are associated with increased birth size of more than 90th centile [24, 25]. The insulin VNTR genes are the other genes that have been implicated in both fetal growth and adult health outcomes [26]. Another study describing a polymorphism in the gene for IGF-I, which is associated with low birthweight showed an increased risk of type 2 diabetes and myocardial infarction, lending support to the hypothesis that genetic variation affecting fetal growth could account for the association between low birthweight and susceptibility to diabetes and cardiovascular disease in later life [27].
In this volume, Hwa et al. [pp. 43–55] outlined the role of the GH-IGF system and the impact of genetic defects of the GH-IGF axis on human linear growth. Defects in the GH-IGF axis leading to postnatal IGF-I deficiency and GH insensitivity syndrome include mutations in the GHR, signal transducer and activator of transcription (STAT5B) and IGFALS (acid labile subunit, ALS) genes. The identification and evaluation of genetic defects in the GH-IGF axis have provided proof of principle and greatly enhanced our understanding of the critical importance of the GH-IGF system in human linear growth. The general prevalence of these specific genetic mutations is however generally low, and could identify only a small proportion of growth defects, therefore suggesting the possibility of other mutations in the promoter or other regulatory parts of the genes that are currently unknown. Moreover, the interaction of these genes with the environment and other signaling pathways such as those affecting the immune system which may affect growth are also just emerging, providing postulations that the GH-IGF axis does not act as an isolated factor in growth disorders. For example, the GHR is a cytokine receptor belonging to the same superfamily of receptors as the interleukins and interferon. All of those receptors signal through the JAK STAT system, so knockout of the STATs affects both GH and cytokine action. Therefore, the blocking of GH action results in growth failure, and the accompanying blocking of the cytokine action may result in immune defects. These observations of how genetic defects in the GH-IGF axis disrupt the ability of the GHR to signal through its JAK STAT pathway and the resulting interaction with the immune system via cytokine signaling may provide an explanation to how chronic inflammatory diseases affecting immune system may impact on growth, highlighting the complex interaction between the GH-IGF axis and other endocrine and immunological processes in the human body to effect growth.

Taken together, these specific genes have only been able to explain a small part of the association with fetal growth and overall metabolic disease risk in future life. It is likely that the association between early-life plasticity and future development of metabolic disorder necessitates a more complex interaction of various factors in utero and environmental influences on a background of genetic predisposition.

**Epigenetic Programming**

Epigenetics is the changes in heritable gene expression caused by alterations independent of changes in the genotype. The main epigenetic mechanisms include DNA methylation and modifications of histones that package the DNA including acetylation. Animal studies have indicated that early-life environmental influences can affect epigenetic changes in the DNA methylation that may
have later life phenotypic consequences [28]. A study utilizing Agouti viable yellow allele mice (Avy), which are obese and hyperinsulinemic, demonstrated that a maternal diet enriched with methyl donors caused hypermethylation in the offspring of Avy mice resulting in the masking of the Avy gene with the offspring being leaner and not hyperinsulinemic [29]. In recent years, a study in humans demonstrated that individuals who were prenatally exposed to the Dutch Winter famine in 1944–1945 had, 6 decades later, less DNA methylation of the imprinted IGF-II gene compared with their unexposed, same sex siblings. The association was specific for periconceptional exposure, reinforcing that very early mammalian development is a crucial period for establishing and maintaining epigenetic marks [30].

In this volume, Netchine et al. [pp. 65–73] described specifically the loss of DNA methylation at the imprinted control region leading to the development of the Russell-Silver syndrome, which is characterized by intrauterine and postnatal growth retardation; in contrast, the gain of such DNA methylation results in Beckwith-Wiedemann syndrome which is characterized by overgrowth syndrome with enhanced childhood tumor risk, providing further validation of how epigenetic processes may affect growth. Godfrey et al. [this volume, pp. 57–63] highlighted the effect of epigenetic processes, in particular DNA methylation, on the risk of developing common non-communicable diseases in later life. Various animal studies have further highlighted role of endocrine and nutritional interventions during early postnatal life in reversing the phenotype in the epigenetic changes, providing the proof of principles that relate maternal nutritional deficiencies and epigenetic changes and the associated phenotypic expression. Although epigenetic processes do offer an additional dimension to elucidating the mechanism underlying early-life exposure and later life health risks, and various animal studies do provide proof of causality on the role of epigenetic changes in phenotypic expressions, the understanding of how nutrition or endocrine interventions may influence epigenetic regulation of genes is only just beginning, and whether these epigenetic changes are markers versus whether they can be causally related to disease outcomes in humans remains to be fully elucidated.

**Other Postulated Mechanisms**

Several other mechanisms have been proposed to elucidate the mechanisms underlying early growth and later life development of metabolic disorders. The maternal glucocorticoid programming is one of these. Studies using animal models have described decreased birthweights in rats prenatally exposed to synthetic glucocorticoids or through inhibition of the placental 11β-hydroxysteroid dehydrogenase type 2 (HSD2) which may induce permanent hypertension, hyperglycemia, and increased hypothalamic-pituitary-adrenal axis (HPA)
activity and behavior resembling anxiety [31]. In humans, 11β-HSD2 gene mutations cause low birthweight and reduced placental 11β-HSD2 activity associated with intrauterine growth retardation. Low birthweight babies were also found to have higher plasma cortisol levels throughout adult life, suggesting HPA axis programming [32].

Maternal hypoxia is another suspected mediator of increased vulnerability to metabolic and cardiovascular diseases [33]. Offspring of mothers who were exposed to a high-altitude environment with chronic hypoxia were growth restricted. Further evidence illustrated the direct detrimental effects of prenatal hypoxia on endothelial function [34], which was independent of maternal nutrition restriction, further supporting the possible role of hypoxia in placental function, fetal growth and metabolic programming.

Placental dysfunction may also play a central role in fetal programming, and the failure of the maternal-placental nutrient supply to match fetal requirements may incite developmental plasticity and adaptations to culminate in the development of metabolic diseases [35]. The basis for this hypothesis stems from the observations that alterations in placental growth and vascular resistance, altered nutrient and hormone metabolism, and changes in nutrient transfer and partitioning between mother, placenta and fetus all have important effects on the fetal adaptations that are thought to be central to programming. The implication of the hypothesis is that optimizing placental structure and function may well have lifelong health benefits for the offspring. Although well described, epidemiological data linking pathological placental changes and development of metabolic diseases in the offspring are currently lacking.

Leptin and the GH-IGF Axis

One of the key components of Barker’s hypothesis described that insulin resistance and associated reductions in muscle mass represent a trade-off between the development of muscle and brain masses under conditions of energetic deprivation in the fetus, with adaptive sparing of the brain tissue at the expense of muscle mass that are ultimately reflected in reduced birthweight [36]. This trade-off, or preferential rationing of energy stores, may be a plausible mechanism ultimately predisposing these individuals to later life metabolic disorders. Many of the other key modulators of energy metabolism including insulin, GH-IGF and the HPA axis are important modulators of fetal growth and birth sizes. In states of chronic energy deficiency, decreased IGF levels and increased GH secretion are often observed [37]. Leptin plays an integral role in signaling energy availability and mediating neuroendocrine response to energy deprivation states in humans. In a study performed on hypothalamic amenorrhea women with chronic energy deficit, a state signified by hypoleptinemia, leptin administration which increased serum leptin
levels to within normal physiological levels after 1 month of treatment was associated with an increase in total IGF-I levels, with a trend to increasing free IGF-I and IGFBP-3 [38], suggesting a key role of leptin in modulating IGF-I and the GH-IGF axis in the energy deprivation state. It is interesting to speculate a possible role of leptin in modulating the GH-IGF system in women in gestation during periods of malnutrition and energy deprivation, and the long-term effects of such modulation on fetal growth and developmental programming. The role of leptin in energy signaling and modulating growth factors especially in gestating women may have implications on possible developmental programming of the fetus of which mechanistic issues remain to be fully elucidated.

**Uncertainties**

The replication of data in different populations and ethnicities proves conclusively that an association exists between early-life and future development of metabolic disorders. Despite postulations put forward to elucidate the mechanism behind the association, it remains inconclusive if these mechanisms are truly causal. It is also possible that the association is the result of the interplay between a multitude of differing mechanisms and influences, both inherent and environmental. It remains uncertain as to how these different mechanisms interact, let alone establishing the predominant factor amongst these differing processes. Moreover, even in the situation where a dominant mechanism truly exists and is causal, it is unknown if such early-life developmental programming will be reversible. If this early-life programming is irreversible, the only available intervention will nonetheless be restricted to a universal effort in improving women’s reproductive health through better nutrition, sanitation and prenatal care. Exhaustive efforts to unravel and debate mechanistic issues behind developmental programming might be relegated to a sterile intellectual exercise with little implications on intervention options to individuals already exposed to poor developmental programming. The relative importance of developmental programming in the pathogenesis of metabolic disorders in comparison to traditional risk factors such as obesity, diet, lack of physical activity, and smoking, also remains unknown.

Nonetheless, the avalanche of data in the last few decades on developmental programming and metabolic disorders has shed new light on the possible pathogenesis of metabolic disorders. Further research will hopefully not only elucidate the causative mechanism underlying such an association, but also allow us to gain insight into the possible interventions we can adopt to curb the ever growing problem of metabolic disorders.


Summary on Drivers of Growth

To summarize the day, we have had 6 outstanding presentations of a very diverse nature, ranging from the sophisticated molecular biology of some of this afternoon’s talks to the sophisticated analysis in nutrition as we saw in some of this morning’s talks, and again I want to acknowledge Nestlé for allowing us to have such a multidisciplinary discussion amongst people who are real experts. I can see 4 or 5 general points that have emerged from the day, and no doubt we will exemplify those in the next 2 days.

First, we have this question about what is normal and what is abnormal – it is very context specific, and it comes very much from the issues of how the different disciplines represented in this room study the human condition. We have groups that look at cohorts or look at normative people and investigate what is different in the range of phenotypes that such individuals have. We have on the other hand the molecular investigation of patients with a particular syndrome, in this case growth failure. I think that there is clearly a need to bridge mindsets between those who look at the issues of normality and those who look at the issues of abnormality. Anthropologists would look at it in a different way to those who use the tools of GWAS. But the kind of epigenetics that Keith Godfrey is involved in — now looking across the range of normative populations in the same way that Maria Makrides and Berthold Koletzko have been looking at normal populations — are focused very differently to what we saw of the work from Irène Netchine and from Vivian Hwa, where they were looking at abnormal populations. The discussion showed that there is some conceptual bridging yet to be achieved. I think that leads to a deeper question about what is normal, and the issue that I would like to emphasize is what is normal fetal development? How do we define that, and in what context? We danced around the issue this morning because the only measure we have generally in fetal development is birthweight and perhaps gestational length (although gestational length is something that we are not very good at assessing, particularly as we have got ourselves into the trap of using ultrasound
to date pregnancies and assume that everybody has normal first trimester growth, which is clearly not so).

Secondly, we were struggling this morning when considering what is normal fetal growth, what is normal birth, is birthweight meaningful, is there some other measure of birth size that is meaningful? And birth size needs to be taken within the context of that population; in that situation it might be very different for a person in rural India or in The Gambia to a person in the United States. And there was a workshop from the WHO some years ago focused on optimizing fetal development – a number of people in this room were at that workshop – and it suggested that we need to recognize that birth size is not a goal in itself, but what we are looking for is ensuring that the child is in optimal state at the time it is born to transition through the next phases of its development, and that will be highly context specific.

The third general theme that came out is about methodology. Here we are in the 21st century struggling with some relatively simple problems such as what is normality, how to feed mothers, and how to feed babies, and we are finding that it is very hard — simple questions turn out to be very complicated. In the final study of maternal nutrition, Maria Makrides gave us a brilliant exposition on the issues surrounding this. Berthold Koletzko did the same about infant nutrition, and you can see that here we are having to have some fundamental rethinking about what is as simple as the basic macronutrient content of food that a baby might be fed. We are uncertain and left with many unknowns because clearly there is something about breastfeeding which in at least an endocrine sense is very different to formula feeding. We have seen the complexities that surround GWAS studies, and I suspect that we are going to find much greater complexities when we consider epigenetics; Keith Godfrey was only giving a hint of the issues that will arise.

And all that leads to the next challenge, which I think everybody involved in developmental science from whatever perspective knows is the real problem. We are dealing with a genome, we are dealing with an epigenome, we are dealing with development — very different passages of development with different critical windows — and we are dealing with subtle changes in the environment which can turn out to have very major effects in the long-term. I don't think we are anywhere near understanding the best ways to integrate all these different perspectives and to fill the knowledge gaps. This is going to be the big challenge to developmental scientists over coming decades, because what we keep on trying to do is reduce very complex systems to simplicity and expect that we will identify a simplistic intervention. Is that really what is going to happen? I doubt it. It is unlikely in my judgment that there will be a singular intervention which will address the problem of trying to give every child on the planet a healthier outcome – we will need more integrative approaches. We have seen some lovely holistic papers this morning, and we have seen some beautiful reductionist science in papers this afternoon. What
we see is that both dimensions are critical to advance our understanding. We are going to have to move to a much more interdisciplinary approach with collaborations across disciplines, and again that is why I am so delighted that there are so many different disciplines represented in this room today.

Peter D. Gluckman
Human Growth: Evolutionary and Life History Perspectives

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Abstract

Evolutionary and life history perspectives allow a fuller understanding of both patterns of growth and development and variations in disease risk. Evolutionary processes act to ensure successful reproduction and not the preservation of health and longevity, and this entails trade-offs both between traits and across the life course. Developmental plasticity adjusts the developmental trajectory so that the phenotype in childhood and through peak reproduction will suit predicted environmental conditions – a capacity that may become maladaptive should early-life predictions be inaccurate. Bipedalism and consequent pelvic narrowing in humans have led to the evolution of secondary altricialism. Shorter inter-birth intervals enabled by appropriate social support structures have allowed increased fecundity/fitness. The age at puberty has fallen over the past two centuries, perhaps resulting from changes in maternal and infant health and nutrition. The timing of puberty is also advanced by conditions of high extrinsic mortality in hunter-gatherers and is reflected in developed countries where a poor or disadvantaged start to life may also accelerate maturation. The postpubertal individual is physically and psychosexually mature, but neural executive function only reaches full maturity in the third decade of life; this mismatch may account for increased adolescent morbidity and mortality in those with earlier pubertal onset.

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Some General Evolutionary Principles

The application of evolutionary thinking to human biology and medicine can be beset by misconceptions. This is because evolutionary processes are not directly concerned with issues of health, disease or longevity but with ensuring successful reproduction. Selective processes operate to maximize reproductive success either directly or indirectly (e.g. through kin selection; see glossary in the appendix), whereas genetic drift and population bottlenecks operate through stochastic processes to exclude some genotypes from successive populations. Selective processes (natural, sexual or social) depend on variation in traits, heritability of some underpinning elements of a trait, and differential reproductive success associated with the trait. Human fitness is to a significant extent determined by survival in the first two decades of life as well as reproductive success following puberty, and is much less influenced by later life events [1]. In contrast, later health and longevity are influenced by such events, exacerbated by the decline in repair processes associated with antagonistic pleiotropy [2].

Key to understanding both macro- and microevolution is the concept of trade-offs. No trait evolves in isolation, and constraints thus exist that limit the range of solutions possible. For example, the size and shape of an animal can be limited by both ecological and energetic constraints, and in the case of terrestrial animals by skeletal constraints [3]. Life history theory considers trade-offs from another perspective, namely the interaction between traits defining a population's life history, and these are discussed below.

Co-evolutionary pressures also need to be considered. Humans did not evolve in isolation from other species; we recognize this well in terms of the defense systems such as stress responses and innate and acquired immunity, and more recently the importance of the gut microbiome to human biology has started to be appreciated. Humans also evolved within social frameworks and with the capacity to create technologies that changed their physical, biotic and social environments. In doing so, potential mismatches between their evolved biology and their environment and lifestyle have been created, and this can affect their health. In recent times, the health impact of such changes with respect to metabolic disease has become particularly apparent.

Microevolutionary processes presumably continue in humans, but the extent to which they are important in a world where technological control of reproduction and survival is widespread, at least in Western societies, remains controversial. One of the problems is that ‘fitness’ is an inclusive concept; it effectively refers to reproductive success which in humans is influenced by both biological and cultural evolution. Estimates of fitness taken from modern populations do not easily distinguish between these two components. The impression gained from an analysis of data derived from the Framingham Heart Study, namely that humans are evolving to be shorter [4], highlights the problems of conflating these concepts. The method of calculation of fitness is sophisticated, but there
can be many reasons why fitness is greater in shorter people. As Nettle [5] has pointed out, fundamental changes in life history strategies are associated with being poor or disadvantaged, and these could be manifest as a relatively greater reproductive success.

**The Role of Developmental Plasticity**

Genotypes do not have a one-to-one relationship with phenotypes. Environmental factors may disrupt phenotypic development, acting as teratogens and leaving the organism to accommodate phenotypically, assuming that the disruption does not lead to loss of viability. With social support and medical technologies, humans can survive to reproduce even with significant developmental disruption, and in that sense phenotypic accommodation can be seen as potentially adaptive [6].

More universally, development is influenced by an ecological range of external environmental influences. In the case of the mammal, a physiological range of maternally created intrauterine environments influences the developmental trajectory such that a range of mature phenotypes can appear. This range is termed the reaction norm, that is the range of environmentally inducible phenotypes that can be elicited from a single genotype. The underlying mechanisms of developmental plasticity include epigenetic change, and are found across all taxa and have the adaptive potential to adjust the phenotype to the actual environment.

We have classified developmental plasticity as being of two types [7]. First is where the adaptive response is closely linked in time to the inducing environments; fetal growth retardation can thus be viewed as an adaptive response of the fetus to a disturbed nutritional environment, and the adaptation is reduced growth to allow it to survive to birth and have the opportunity to reproduce. The second and more frequent form of adaptive developmental plasticity need not induce immediate responses, rather the phenotypic difference appears later in the life course. For example, it is now apparent that relatively unremarkable changes in maternal nutrition can induce phenotypic changes in the offspring which emerge some time after birth [8]. Such developmental programming can be seen as adaptive if it can enhance the potential of the individual to reproduce successfully. We termed this type of response a predictive adaptive response, because the adaptation is made in anticipation of a predicted later environment where a particular range of phenotypic traits is anticipated to be more advantageous to fitness [9]. Bet-hedging is an alternative strategy used in fast-reproducing organisms to enhance fitness in variable environments [10]. In contrast, where the environmental change is in the order of generation times, and particularly in species with a low number of offspring such as the human, modeling shows that even somewhat inaccurate predictions offer a fitness
advantage [11]. It is important to reiterate that the adaptive responses of importance are those that occur during childhood and the early reproductive years if they are to promote successful reproduction [1]. Later life consequences need not be adaptive.

Evolution is to a large extent blind to what happens later in life. Thus early life insulin resistance may be an adaptation of advantage to allow metabolic survival and promote accelerated maturation in nutritionally poor circumstances; however, this response later in life may be maladaptive if the prediction is wrong and the nutritional environment is obesogenic – this will be manifest as metabolic disease. In this situation, the metabolic disease is a consequence of the mismatch between the predicted environment and the actual environment, but the adverse health consequences are likely to occur only after peak reproduction and thus are of little consequence to fitness. Indeed in our evolutionary past, developmentally induced insulin resistance would have been of little consequence given the low likelihood of exposure to an obesogenic environment.

This delayed anticipatory response may occur in association with, or in isolation from, more immediate adaptive responses. For example, children who are born small are more likely to have permanent growth retardation. The initial growth retardation is an immediate adaptive response, while the persistent growth failure in childhood and stunting can be envisaged as a predictive adaptive response to anticipated nutritional deprivation. The apparently delayed obesity and insulin resistance in children born small [12] can be similarly interpreted as a predictive response in association with the immediate fetal growth response. The recent observation of an increased risk of obesity in adults who were first-born children [13] highlights how subtle developmental influences (the increased maternal constraint associated with primiparity) can induce predictive adaptive responses, in this case a metabolic phenotype more appropriate for a lower nutritional plane than mismatched in an obesogenic environment. There is growing evidence for the central role of epigenetic mechanisms in adaptive developmental plasticity [14].

**Life History Theory**

Life history theory considers the evolution of, and the trade-offs between, traits directly related to reproductive success. This evolved suite of traits defines the basic characteristics of a species: their patterns of growth and maturation, their longevity and phases of development, the number of offspring they have and so forth. Such considerations cannot be isolated from the ecology of the species and the social structure of the population. Subject to nutrient availability, being large as an adult is in general an advantage for survival, but growth takes time. Thus, the longer it takes to reach the age of maturation,
the greater the risk of dying before reproducing. Consequently, a key trade-off is that between investing to grow larger and investing in reproduction. Similarly, there is a trade-off between the quality and number of offspring that themselves need to survive to reproduce. In addition, there is a further trade-off between current and future reproduction – in humans this can be manifest in the lower viability of offspring associated with shorter inter-birth intervals. It is important to emphasize that evolution can only act on traits that vary and have a heritable element. There is an extensive literature on the evolution of life history traits [15].

**Heritability, Genetics, Non-Genetic Inheritance and Phenotypic-Driven Evolution**

Heritability is a concept which, while often used to reflect genetic determinism, simply refers to the extent to which phenotypic variation can be explained by intergenerational influences. Certainly, the genetic basis of heritability is dominant, but is not the only factor. Estimates of heritability are dependent on the environment of the lineage – the heritability of height is far greater in conditions of high nutrition than in those of changing or poor nutrition where stunting may affect different generations/individuals to different extents. There is increasing interest in the role of non-genomic inheritance through trans-meiotic passage of epigenetic marks, or indirectly through mechanisms which lead to the recreation of the inducing environment in each successive generation [16]. For example, stunted women are more likely to give birth to children who are small because of greater maternal constraint, and children who are born small are themselves more likely to grow up to be small, particularly if the environment remains disadvantageous. The less than optimal intrauterine environment may thus induce epigenetic changes in the offspring which are again induced in successive generations, but the epigenetic mark has not passed meiosis. West-Eberhard [17] in particular drew attention to the potential for developmentally induced changes to be fixed in a population by the poorly elucidated processes of genetic assimilation, which may play a role in evolutionary processes [6].

**An Evolutionary and Life History Perspective on Human Growth**

The human life course and patterns of growth and development must be understood in the context of the above discussion. However, one of the difficulties of applying evolutionary biology to human biology and medicine is that while it is easy to develop evolutionary arguments and hypotheses, testing such hypotheses is in general indirect. Nevertheless, a conceptual framework for doing so does exist [18].
The human can be characterized as a long-lived species that has low fecundity, a long pre-reproductive phase compared to the life span, with relatively altricial offspring who have a high dependence on its parents for many years after birth. It is also a generalist species capable of living successfully in a range of ecological environments, and one with particular potential to undergo rapid cultural evolution as a result of its capacities for language, social structure and technology.

The hominin clade has been bipedal for perhaps at least 4.4 million years. As the hominin clade has evolved, it has grown in stature such that skeletal remains of *Homo erectus* members who lived some 1.8–1.3 million years ago suggest a final height of between 150 and 185 cm. But perhaps of greater importance in understanding the human life history has been the growth of the human brain from a volume of about 450 cm³ in the earliest *Australopithecines* to about 1,250 cm³ in modern *Homo sapiens*. The development of a bipedal gait, the adaptive advantage of which remains speculative, requires a relatively narrow pelvis to be able to run, and this presumably had adaptive advantage both for hunting and escaping predators. But the human infant cannot be delivered through the pelvic canal at the same level of brain maturity as are other primate infants born to quadripedal mothers with a wider pelvis. Thus there has been a trade-off—the human life history is based on secondary altricialism, that is giving birth to very dependent immature offspring, at a shorter gestational length and thus smaller head size. This prolongs the time of absolute dependence of the offspring on its mother for mobility and sustenance. In turn this may have played a role in the development of the human social structure, which in turn allows for infants to be well supported through this period of immaturity. There is evidence relating the complexity of human social structure to mature neocortical and thus total brain volume [19]. In comparison to other members of the primate clade, a larger proportion of human brain growth occurs postnatally, and this in turn may provide an explanation for why humans are the fattest mammalian species at birth. Kuzawa et al. [20] have suggested that neonatal and infant obesity is an adaptation to provide a metabolic buffer for the brain in infancy, when diarrhea or malnutrition may otherwise threaten brain development. In this regard, it is interesting to note that infantile adiposity falls at about the age when infants are presumed to have been weaned in the Paleolithic.

Gestational length itself is subject to environmental effects. There is evidence for example that maternal nutritional state at conception can influence gestational length, with mild undernutrition associated with longer gestational length and more severe undernutrition with shorter gestational length. Pediatricians have long recognized the relatively precocial maturation of mildly premature infants. This suggests that in the event of nutritional stress, the fetus can accelerate its maturation and shorten its gestational length in the anticipation that a longer pregnancy is more likely to lead to intrauterine death. The potential adaptive advantage to both mother and fetus is apparent.
Humans have relatively short inter-birth intervals given this prolonged period of infant dependency, and this provides a fitness-enhancing strategy because fecundity is relatively greater. However, this is only possible because the social structures allow weaning to occur before the infant is able to fend for itself nutritionally and in other ways, but yet can be supported by adults. This demonstrates how the evolution of human life history has been influenced by the evolution of social structures, and vice versa.

Bogin [21] divides the prepubertal period of *H. sapiens* life cycle into three phases: infancy, childhood and the juvenile phase. In turn, he and Hochberg [22] have related these phases to distinct transitions in growth. In this model, infancy is seen as a continuation of the fetal period of growth; the rate of linear growth has started to decline in fetal life and while still rapid is declining through infancy, lasting until weaning. Based on contemporary hunter-gatherer societies, this is assumed to have been generally between 2 and 3 years of age. However, the endocrine control of growth changes during that period, with growth hormone dependency emerging in the first year of life [23]. Further, Karlberg [24] would argue that phases of growth as illustrated by the infant-child puberty model of growth show a transition from the infant to childhood phase earlier than that suggested by the timing of weaning. This simple debate highlights the difficulties of directly linking one aspect of maturation to a particular single circumstance; life history itself represents the outcome of a set of trade-offs to optimize fitness.

Childhood is generally defined by the period between weaning and adrenarche [25] and is a period of continued parental dependency. A key component of this phase is the replacement of deciduous teeth with permanent teeth – by adrenarche the first four molars have generally erupted. The period between adrenarche and the onset of puberty is increasingly recognized as a distinct phase of development, termed the juvenile period. In behavioral terms, the juvenile has some level of independence but is neither reproductively competent nor socially independent; a similar phase is also seen in many other species. In the human, brain size is maximal by the start of the juvenile period, although brain maturation continues into the third decade of life [26]. It has been frequently suggested that this is a critical phase for developing social skills for living in a group. But earlier experiences can also influence the development of such executive functions.

It has been suggested that prolonged childhood is a unique feature of the human life cycle [21]. In part, this apparent prolongation may simply reflect the relatively short infantile phase which allows the mother to reproduce earlier and thus increase her fitness. It also reflects the longer duration of postnatal brain growth which is not complete until the end of the childhood phase, which is in turn a reflection of both the secondary altricial nature of human gestation and the relatively large mature brain size of humans.
**Puberty**

In life history terms, survival to the age of pubertal maturation allows the individual to reproduce; we have discussed above the trade-off between the age at reproductive maturation and mature body size across species. The timing of puberty shows considerable variation within and between human populations, and this plasticity may be adaptive in that it allows a number of developmental factors to influence the timing of puberty. Two uncertainties enter this discussion: the longevity of humans in evolutionary history, and thus, the timing of puberty. While the average life expectancy in the Paleolithic is generally thought to have been low (perhaps 25 years at birth, or about 35 years if one survived infancy), there is ample paleological evidence suggesting that a significant number of individuals did survive into the sixth and seventh decades of life. Arguments over the evolutionary origins of the menopause, not the topic of this paper, rely in part on the assumption of there being a fitness advantage of living into old age; that generates an indirect fitness effect of the grandmother assisting her daughters with their mothering duties, thus promoting grandchild survival.

There is much more uncertainty over the timing of puberty in the Paleolithic. Based on the timing of the third molar (M3) eruption, which in other primates is generally at the time of sexual maturation [27], it has been generally stated that humans evolved with the age of pubertal completion late in the second decade of life. However, if in the Paleolithic where the average life expectancy is shorter, perhaps the age of M3 eruption and pubertal maturation became disassociated. Given the high risk of not surviving to reproduce, an earlier age of puberty would have had a beneficial fitness effect. Evidence to support this comes from a study of extant hunter-gatherer populations which demonstrates a broad range of ages at menarche, including some with menarche at as low as 13 years of age [28]. Such studies have their limitations, even though they are often used to extrapolate backwards into evolutionary time, but the finding that the age at menarche inversely correlated with the chances of surviving to the age of 15 in these populations does support the hypothesis that earlier maturation is an adaptive plastic response to situations of high mortality. These studies also suggest, along with observations of the secular trend in the declining age at puberty and the effect of migration in infancy, that the reaction norm for the age at puberty extends to a young age. This likely reflects the protection of the capacity to respond in this way, and suggests previous periods of young pubertal ages across evolutionary time.

There is a well-documented secular decrease in the age at puberty in females based on the timing of menarche [29]; more recently a similar trend in the male has been documented by the declining age of peak pubertal growth spurt [30]. In historical terms, this appears to reflect the increase in child health and nutrition during the late 18th century, but it may actually be driven in part by the change in maternal nutrition and early developmental effects, as recently
demonstrated by accelerated puberty in the rat following enhanced maternal nutrition [31]. Given that child health likely declined following the development of agriculture and increasingly dense urban living, we have suggested that the secular trend may be taking human maturation back to what it was during the Paleolithic [32].

The plasticity of human maturation is highlighted by the evidence of prenatal and postnatal nutritional and postnatal stressor influences on the age of puberty. Puberty is accelerated by prenatal undernutrition, as reflected in low birthweight, in both humans [33] and rats [31] and by postnatal stress [34]. Relative adiposity in the juvenile period is associated with accelerated puberty particularly if low birthweight is also present [33]. The most obvious manifestation of this is in the very early puberty seen in children who migrated from underdeveloped countries to Western environments in infancy [35]. Such patterns of maturation can be interpreted in evolutionary and life history terms using the predictive adaptive framework, as children who start their life predicting a high risk of extrinsic mortality accelerate their maturation to reduce that risk and increase the likelihood of reproducing. The predictive model makes it more likely that such children will become obese if exposed to an obesogenic environment. Conversely, if there is juvenile undernutrition, puberty is delayed in the expectation that the delay may allow nutritional circumstances to improve and thus allow the mother-infant dyad a better chance of survival. Similar arguments can be developed for pubertal responses to abuse and deprivation in infancy.

It has been suggested that the pubertal growth spurt is unique to humans. But sexual dimorphism becomes exaggerated or appears in many mammals during puberty. Indeed, skeletal and body size changes are common in many mammals during puberty. The key difference is that in humans, linear growth is the most obvious change, although human puberty as in other species is also associated with gender-dependent changes in body composition. While the growth spurt is particularly prominent in the human, this may be the inevitable outcome of bipedalism. All other primates are quadrupedal, and the simple mechanical differences in how increases in body size might affect locomotion may constrain such increases in size, which are important to fitness – the increase in body size being largely linear in humans and more cuboidal in other species. It is clear that large body size provides a fitness advantage to males due to its impact on sexual competition, and in females it provides greater likelihood of successful support of pregnancy.

The relative roles of natural and sexual selection in determining pubertal growth patterns and the development of sexual characteristics remain speculative. Presumably sexual selection played a significant role in the patterns of hair distribution and the development of body shape. The nature of adult body proportions in different members of the Homo genus has been the subject of extensive study by paleoanthropologists and by those who have used climatic
and environmental arguments to posit explanations for the very different body shapes and sizes seen across modern human populations. For example, adaptive changes in response to cold exposure have been suggested as the basis of shorter limb length and flattened nasal and facial shape in populations living in very cold climates, such as the Inuit.

Thus, while the pubertal linear growth spurt is essentially unique to the hominin clade and probably evolved in early Homo species, puberty itself is a prolonged process in other primates. There remains a period of ongoing maturation which, depending on the reproductive strategy of the species, can extend for some time before the role as an adult is completely established. But it is particularly in the modern human that this prolonged phase of behavioral maturation extending beyond physical puberty becomes prominent.

**Adolescence**

While puberty is a solely biological process, the completion of adolescence is both biological and cultural. We have defined adolescence as being completed when the individual is fully accepted as an adult within society. The extent to which such acceptance is a biological and/or a social construct is not resolved. We now know that in Western societies, neural executive function is not fully mature until the third decade of life. This is reflected in structural changes in the frontothalamic pathways which extend well into the third decade [26]. During this period of postpubertal adolescence, the individual is exposed to a mature endocrine milieu and has a relatively mature body habitus, but has immature self-control and emotional control and the ability to show judgment is incompletely matured. Risk taking behaviors in this period are enhanced [36]. This postadolescent phase appears to have become particularly prolonged in recent decades, in part because the age at puberty has fallen and in part because in Western societies the age of acceptance as an adult has risen.

The key evolutionary question here relates to the age of full maturation of frontothalamic pathways. Is it that in the evolutionary past the age of brain maturation was the same as it is now, but in the simpler social conditions of clan societies, the advanced functions were of lesser importance and the individual was accepted as an adult at an earlier age? Is it that the period required for frontothalamic maturation takes longer in a more complex modern society? Or that some aspect of how infants and children are reared in modern societies delays maturation of frontothalamic pathways? We have raised the question of whether the shift in focus of early childhood experience from executive function (social) learning to cognitive learning may play a role [37]. These questions are amenable to empirical study and are of importance because the answer has practical implications. It is reported that children with earlier ages of puberty, that is with greater mismatch to their sociological environment, have far greater
morbidity in adolescence – for example the rate of attempted teenage suicide is much greater in boys who have an earlier age of puberty [38]. Girls who have menarche at a very early age have a greater likelihood of developing eating disorders [39].

**Final Remarks**

Physicians are used to thinking about their patients in proximate terms – that is the mechanisms and causes of disease – in a manner that leads to direct therapeutic intervention. But as this paper has suggested, there is a second layer of interpretation needed – that of understanding ultimate causation in evolutionary and phylogenetic terms – if we are to have a full understanding of the human condition [40]. A life history perspective gives valuable and utilitarian insights into the understanding of growth, both in terms of skeletal growth and body composition and in terms of functional maturation of the individual. But as Nettle [5] has recently noted, a life history perspective also allows a broader interpretation of many aspects of human reproductive biology and behaviors in populations who are disadvantaged.

**Appendix**

*Glossary of Evolutionary Terms Used*

*Adaptation* – refers to the selection of a trait which has been shown to have a fitness advantage. This is a difficult test, and is often inferred rather than proven from data suggesting that the trait promotes the organism's (and its offspring's) survival and reproduction in the environment in which they live.

*Antagonistic pleiotropy* – a selected trait may have beneficial effects that promote fitness in early life but may incur costs later in life.

*Fitness* – generally refers to the successful survival and reproduction of an organism allowing gene flow to the next generation.

*Genetic drift* – refers to the stochastic nature of the chances of an allele being passed onto the next generation. At a population level, it leads to changes in gene frequency not based on selection.

*Heritability* – the degree of phenotypic variation which can be accounted for by intergenerational influences. In quantitative genetics, it refers to the ratio of genotype-induced variance to the total phenotypic variance of a population.

*Kin selection* – the concept where an organism adopts evolutionary strategies that promote its relatives' fitness, even if it is at the expense of its own individual fitness. It is based on the idea that an organism shares a greater proportion of its genes with a relative than with another unrelated organism; hence, it may operate particularly in social animals wherein a high degree of relatedness is present.

*Maternal constraint* – maternal and uteroplacental factors that modulate fetal size. This limits fetal growth to allow birth through the narrow pelvic canal.
Microevolution – evolution of altered characteristics within a species due to genotypic and phenotypic change.

Macroevolution – evolution of a species; essentially an accumulation of microevolutionary change resulting in reproductive isolation between populations.

Natural selection – the process by which natural variation in a trait affects survival and fitness and leads to alterations in gene frequency within a lineage over time.

Phenotypic accommodation – phenotypic adjustment in response to a developmental disruption.

Pleiotropy – the gene product of a locus having multiple effects on physiology and phenotype.

Predictive adaptive responses – the usage of environmental cues by a developing organism to forecast the future environment and to attempt to match its physiology accordingly by modulating its developmental trajectory.

Reaction norm – the range of phenotypes that can be induced from a single genotype upon responding to variation in the developmental environment.

Sexual selection – a form of selection in which genes underlying a trait that is present in an organism that is sexually preferred – either because of intra-gender conflict or mate choice – become concentrated in the population over time.

Social selection – a form of natural selection similar to sexual selection where the preferred characteristics for mate choice reflect eusocial characteristics.

Trade-off – a situation where change in one trait benefits the organism (generally by increasing fitness) but concomitantly incurs a cost in another trait.

Acknowledgements

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Secular Trends in Birthweight

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Abstract

From the mid- to late 20th century, average birthweight increased in many countries, including the United States. However, more recent data now suggest that mean birthweight has begun to decline. The most recent US data indicate that in 2008, compared with 1990, about half as many babies were macrosomic at birth (≥5,000 g), whereas there was a 17% increase in low birthweight (<2,500 g). Part of the observed decline in birthweight likely relates to decreases in gestation length and corresponding increases in rates of preterm and early term birth over the past several decades. However, available data suggest that fetal growth has also declined independent of gestational age at birth. Since 2000, rates of small for gestational age have increased, whereas rates of large for gestational age have decreased. Declines in birthweight and macrosomia are most likely largely explained by decreases in gestation length, itself caused by obstetric interventions, especially induction of labor and to a lesser extent elective cesarean delivery. However, it appears that fetal growth is also declining, at least in some settings, independent of gestation length. Reasons for this decline are as of yet unexplained and merit further investigation.

Introduction

According to the popular press and public perception, babies are becoming bigger and bigger at birth. For example, the July 2011 birth of a 16 pound, 1 ounce baby in Texas sparked extensive news coverage and editorials regarding the 'steady upward trend in birthweight' and 'alarming' increase in rates of macrosomia [1, 2]. In addition to its ability to sell newspapers, birthweight matters because it is a marker of maternal health and health care as well as an important predictor of both short and longer-term child health outcomes [3].
Lower weight at birth is associated with higher risks for neonatal morbidity and mortality among both term and preterm infants [4], and high birthweight predicts cesarean delivery, shoulder dystocia, and newborn hypoglycemia. In later life, individuals born at lower birthweights have higher risks of type 2 diabetes, hypertension, cardiovascular disease, and mental illness, whereas those born at higher birthweights are more likely to develop obesity and breast cancer [5–8].

From the mid- to late 20th century, average birthweight increased in many countries, including the United States [9–11], Canada [11–15], the UK [16–18], Scandinavia [19–21], China [22, 23], and Japan [24]. These increases have been attributed to greater fetal growth resulting from improved prenatal care, lower rates of smoking and teen pregnancy, and secular increases in maternal pre-pregnancy weight, gestational weight gain, and gestational diabetes mellitus [13, 25]. Many of these factors have continued to follow the same trajectories since the 1990s. However, more recent surveillance data now suggest that mean birthweight has in fact begun to decline in the US [26] and other developed countries. Part of the observed decline in birthweight likely relates to recent decreases in mean gestation length and corresponding increases in rates of preterm birth over the past several decades [26–30]. As gestation length and fetal growth (birthweight for gestational age) have different determinants and sequelae [31], it is important to disentangle their relative contributions to trends in weight at birth.

In this paper, I will summarize evidence regarding trends in birthweight, with a focus on the past 20 years. I also include data on trends in both high birthweight (macrosomia) and low birthweight. I also review contributors to birthweight, including gestation length and fetal growth, their contributors, and their trends over time. I primarily focus on data from the United States, but also include published studies from other developed countries.

**Trends in Mean Birthweight, Low Birthweight, and High Birthweight**

Prior to 1990, abundant evidence suggested that birthweight was on the rise. For example, using birth certificates from infants born in Illinois in 1950–1990, Chike-Obi et al. [10] observed a trend towards higher birthweights including increases in the mean, mode, and upper end of the birthweight distributions. This rightward shift was especially evident among children (born 1989–1991) whose parents (born 1956–1976) were also included in the dataset (fig. 1), indicating that demographic trends such as immigration did not explain the increase [10].

However, these curves have now switched places (fig. 2). In 2005, compared with 1990, the range of birthweights was lower among all infants born in the US [28, 32]. The most recent data indicate that in 2008, compared with 1990, about half as many babies were macrosomic at birth (≥5,000 g; table 1), whereas there was a 17% increase in low birthweight (<2,500 g).
Similar trends have been seen outside of the United States. Canada has experienced similar increases in low birthweight [33], although some areas have experienced increases in birthweight [34]. In France, birthweight increased until about 1995, and subsequently decreased thereafter. By 2003, mean birthweight among term births in France had decreased back to a level last seen in 1972 [35].
In Queensland, Australia, both birthweight and term macrosomia increased from 1988 to 2001, and subsequently dropped to 2005 [36]. In Denmark, birthweight increased steadily from 1970 to about 2000, and subsequently declined [37]. Unfortunately, the authors present macrosomia rates grouped in 5-year intervals, so it is impossible to determine whether similar declines were evident after 2000. Interestingly, although these studies both suggest a U-turn in birthweight and macrosomia trends by the late 1990s, the study authors apparently did not see, or discounted, the reversals. Both Lahmann et al. [36] and Schack-Nielsen et al. [37] concluded that both mean birthweight and the prevalence of high birthweight increased steadily during the entire period studied.

In China, Liu et al. [23] had previously reported increases in mean birthweight and rates of macrosomia (from 2.6 to 13.2%) between 1970 and 1999. More recently, however, Han et al. [38] reported decreases in mean birthweight from 1987 to 2006, among both boys (3,227–3,051 g) and girls (3,268–3,027 g) in Henan province. Both low birthweight and very low birthweight increased during the same period, whereas macrosomia decreased. Similarly, in Southern China, Lu et al. [39] found that the rate of macrosomia rose from 6.0% in 1994 to 8.5% in 2000, and subsequently decreased to 7.8% in 2005. Similar turnarounds were observed in mean birthweight trends. The Republic of Korea has also reported increases in rates of low birthweight among singleton births since 1995 [40]. Japan, however, has reported a decrease in birthweight and increase in rates of low birthweight dating back to the 1970s [41].

What could be accounting for these recent, unexpected, and apparently worldwide decreases in birthweight? To understand these trends, it is important


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<td>&lt;1,000</td>
<td>0.63, 0.72, 0.70</td>
<td>14, 11, –3</td>
</tr>
<tr>
<td>1,000–1,499</td>
<td>0.65, 0.76, 0.75</td>
<td>17, 16, –1</td>
</tr>
<tr>
<td>1,500–1,999</td>
<td>1.33, 1.63, 1.58</td>
<td>23, 20, –3</td>
</tr>
<tr>
<td>2,000–2,499</td>
<td>4.37, 5.15, 5.14</td>
<td>18, 18, 0</td>
</tr>
<tr>
<td>2,500–2,999</td>
<td>16.03, 18.44, 18.57</td>
<td>15, 16, 1</td>
</tr>
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<td>3,000–3,499</td>
<td>36.71, 38.87, 39.20</td>
<td>6, 7, 1</td>
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<tr>
<td>3,500–3,999</td>
<td>29.40, 26.61, 26.41</td>
<td>–9, –10, –1</td>
</tr>
<tr>
<td>4,000–4,499</td>
<td>9.10, 6.75, 6.60</td>
<td>–26, –27, –2</td>
</tr>
<tr>
<td>4,500–4,999</td>
<td>1.59, 0.96, 0.92</td>
<td>–40, –42, –4</td>
</tr>
<tr>
<td>5,000 g or more</td>
<td>0.19, 0.11, 0.10</td>
<td>–42, –47, –9</td>
</tr>
</tbody>
</table>

Adapted from Martin et al. [3].
Birthweight Trends

Gestation Length and Its Determinants

Length of gestation is the most important predictor of size at birth [42]. In the United States, the rate of preterm birth (i.e. births before 37 completed weeks of gestation) has increased over the past 2 decades. From 1990 through 2006, preterm births increased steadily from 10.6 to 12.8%, a 20% increase (table 2) [3]. During the same period, the early preterm rate (birth at <34 weeks) increased modestly by 9%, whereas the late preterm rate (34–36 weeks) climbed by 20% (table 2). However, after 2006 both early and late preterm births decreased, back down to 12.3% in 2008 [3].

Mothers under age 15 and aged 45 and over are most likely to have a preterm delivery [3]. Preterm rates for these youngest and oldest mothers are about twice those of mothers aged 25–34 years. The preterm rates for older women are strongly influenced by their greater likelihood of having a multiple birth, itself a strong predictor of gestation length. However, trends in singleton preterm births have paralleled those for preterm births overall, with an increase from 1990 (9.7%) to 2006 (11.1%), and subsequent decline to 2008 (10.6%) [3]. Furthermore, although births to older mothers have been increasing, rates of teen pregnancy have declined substantially over time [3]. Other drivers of preterm birth in developed countries include cigarette smoking and low maternal pre-pregnancy weight [42], both of which are also increasingly less common.

Term births (37–41 weeks) have traditionally been viewed as a homogenous group. There is, however, growing evidence of increased neonatal morbidity

Table 2. Percent distribution of US births by gestational age, in 1990, 2006, and 2008

<table>
<thead>
<tr>
<th>Percent of total births</th>
<th>Percent change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total under 28 weeks</td>
<td>0.71  0.76  0.74</td>
</tr>
<tr>
<td>Total under 34 weeks</td>
<td>3.32  3.66  3.56</td>
</tr>
<tr>
<td>34–36 weeks</td>
<td>7.30  9.15  8.77</td>
</tr>
<tr>
<td>Total under 37 weeks</td>
<td>10.62 12.80 12.33</td>
</tr>
<tr>
<td>37–38 weeks</td>
<td>19.66 28.89 27.85</td>
</tr>
<tr>
<td>39 weeks</td>
<td>21.72 25.43 26.62</td>
</tr>
<tr>
<td>40–41 weeks</td>
<td>36.68 27.20 27.52</td>
</tr>
<tr>
<td>42 and more weeks</td>
<td>11.33  5.67  5.68</td>
</tr>
</tbody>
</table>

Adapted from Martin et al. [3].
among early term (37–38 weeks) infants compared with those born full term (39–41 weeks) [43, 44]. In response, organizations such as the March of Dimes are recommending that researchers differentiate between ‘early term’ and ‘full term’ births [45]. Trends in early term births have paralleled those of preterm births, with increases from 1990 to 2006, followed by a recent slight decrease (table 2). Conversely, late-term births, those after 41 completed weeks, have dropped dramatically, with an almost 100% drop over the past 2 decades.

Predictors of late preterm and early term birth are likely to differ from predictors of early preterm birth. Much of the increase in births at 35–38 weeks may well be iatrogenic, as ‘indicated’ and elective cesarean deliveries as well as induction of labor account for an increasing proportion of births in the US [3, 29, 43]. As many as 28–36% of scheduled deliveries occurring before 39 weeks are elective, i.e. scheduled in the absence of medical or obstetrical indications [46]. Similar trends in both gestation length and obstetric interventions have been seen many other countries as well [38, 47–49].

Whether trends in obstetric practice entirely explain those in gestation length remains uncertain, however. Cesarean deliveries have not varied in parallel with gestation length. The proportion of cesarean deliveries decreased throughout the early 1990s, and has steadily increased from 1996 to 2008 [3]. Although the rate of increase has slowed during the past few years, no decrease is yet apparent that could explain the recent flip in gestation length trends. Induced labor steadily increased throughout the 1990s and into the early 21st century. In an ecologic analysis of US birth certificate data, Zhang et al. [29] concluded that increasing use of labor induction was a likely cause of declines in gestation length from 1992 to 2003. Unfortunately, national surveillance reports do not include the most recent trends in labor induction to help understand the most recent increases in gestation length. Some data do suggest that early term deliveries may be starting to wane. After a regional health care system in Utah implemented guidelines in 2001 to discourage early term elective deliveries, the prevalence of near-term elective deliveries decreased from a baseline 28% of all elective deliveries to less than 10% within 6 months, and after 6 years continued to be less than 3% [50]. In 2007, the American College of Obstetrics and Gynecology published an opinion recommending against elective cesarean delivery prior to 39 weeks [51], which may result in similar practice changes nationwide.

However, even among spontaneous vaginal births, the distribution of gestational ages has shifted to the left [28, 30]. In an analysis of US term singleton births, Donahue et al. [28] found that declines in gestation length from 1990 to 2005 were strikingly similar regardless of route of delivery or whether labor was induced (fig. 3). Similar trends were also apparent among a homogenous ‘low risk’ subgroup, defined as women who were 25–29 years old, non-Hispanic white race/ethnicity, greater than 12 years of education, married, received prenatal care in 1st trimester, non-smoker, no medical complications during current or previous pregnancy, delivered vaginally, labor not induced, had an ultrasound, and
gained 26–35 pounds during the current pregnancy (fig. 3). These findings suggest that demographic shifts in the population and trends in obstetric care are not likely to be entirely explaining the declining gestational age among US births.

More relevant to the current topic, however, is whether trends in gestation length, whatever the cause, can explain the observed trends in birthweight. To address this question, it is necessary to examine trends in fetal growth independent of gestational age at birth.

**Fetal Growth and Its Determinants**

Fetal growth is typically defined as birthweight for gestational age, and typically reported as a percentile or z score within a given week of gestation compared with a sex-specific population reference [31]. Small for gestational age (SGA) is usually considered to be birthweight for sex and gestational age below the 10th percentile, and large for gestational age (LGA) as birthweight for sex and gestational age above the 90th percentile, although other definitions exist [52].

In addition to sex, other determinants of fetal growth include maternal racial/ethnic origin, height, pre-pregnancy weight, gestational weight gain, parity and weights of prior births, general morbidity and episodic illness, alcohol
and tobacco use, and paternal weight and height [31, 42]. Because many of these factors, including race/ethnicity, birth order, and siblings' birthweights, are not modifiable, some have recommended the use of 'customized' birthweight percentiles [53]. However, others have argued that since maternal characteristics account for only a small percent of the total factors influencing birthweight, and since customized percentiles are unable to distinguish between pathological and physiological influences of maternal characteristics on birthweight, the best estimate of an infant's optimal birthweight remains close to the population average [54]. Furthermore, while these factors may be important for assigning a fetal growth percentile to an individual infant, they are less relevant to population trends, especially if the characteristics of mothers do not dramatically change over time, or are accounted for in analysis. Most analyses reporting trends in fetal growth have not used references customized to maternal characteristics. However, it is essential to account for infant sex and plurality, given their strong contributions to fetal growth.

Compared to the more numerous papers with information on birthweight trends, fewer papers provide information regarding trends in fetal growth among singletons. However, available data do suggest that fetal growth has declined independent of gestational age at birth. Donahue et al. [28] found that, as birthweight decreased, rates of SGA increased among term singleton births from 1990 to 2005, especially after 2000, whereas LGA decreased during this same period. Birthweight decreased within each week of gestation, further evidence that decreases in gestation length did not fully explain the observed birthweight trends. Table 3 shows similar trends of SGA and LGA, by sex, among all singleton US births. Although SGA and LGA rates differed by race/ethnicity, trends over time were similar in all groups. In contrast, however, and using the same dataset, Zhang et al. [29] reported decreases in SGA and increases in LGA over a similar time period. A likely explanation for this discrepancy may be the use of gestational age determination by last menstrual period vs. clinical estimate.

Maternal weight and gestational weight gain are two important contributors to offspring size at birth that have both shown dramatic increases over the past two decades, in the US and worldwide [25, 55–58]. Both factors contribute to risk for gestational diabetes mellitus, which itself promotes fetal growth [3]. Smoking, which predicts poor intrauterine growth, has been on the decline. The ongoing trends in these factors should, if anything be spurring increases in fetal growth, rather than the recently observed decreases. In the paper by Donahue et al. [28], the maternal characteristics routinely recorded on the birth certificate did not appear to be responsible for observed decreases in fetal growth. This observation was concordant with the fact that the directions of trends in all maternal characteristics have continued since the early 1990s without any reversals. Since these trends explained past increases in birthweight and fetal growth, they could not explain recent decreases. Although maternal pre-pregnancy body mass index (BMI) was not available in this dataset, accounting for increasing pre-pregnancy
BMI trends should adjust fetal growth estimates even further downward. Similarly, accounting for route of delivery or induction also did not explain the trends.

In France, trends in SGA and LGA were also consistent with the trend in mean birthweight: there was a marked decrease in SGA between 1972 and 1995, whereas between 1995 and 2003, an increase in SGA and a decrease in LGA were observed [35]. The decrease in fetal growth after 1998 could not be explained by adjustment for induction of labor, maternal weight or weight gain, or any other available measure [35]. However, the method of gestational age determination in the French dataset evolved over time, and this methodological difference may account for part of the observed fetal growth trends.

### Discussion

What might account for these recent, unexpected, downwards trends in infant size at birth? Increases in multiple gestation are not the cause, since trends are the same among singletons only. Trends in maternal characteristics such as prepregnancy weight, gestational weight gain, and smoking should, if anything, promote even greater fetal growth over time. Some authors have speculated that routine testing for and improved treatment of gestational diabetes mellitus might provide an explanation [25, 59]. However, fetal growth has apparently declined also among infants born to non-diabetic mothers.

Gestation length is clearly an important factor. While obstetric practice, especially induction of labor, likely accounts for observed decreases in gestation length and at least part of the decline in birthweight and macrosomia, it is not likely to explain the decrease in fetal growth entirely. If babies with higher fetal growth percentiles were over time more likely to be delivered earlier in

<table>
<thead>
<tr>
<th></th>
<th>Percent of total births</th>
<th>1990</th>
<th>1995</th>
<th>2000</th>
<th>2005</th>
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<tbody>
<tr>
<td><strong>SGA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>10.5</td>
<td>10.5</td>
<td>10.2</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>10.7</td>
<td>10.5</td>
<td>10.1</td>
<td>10.5</td>
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<tr>
<td><strong>LGA</strong></td>
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</tr>
<tr>
<td>Boys</td>
<td>11.1</td>
<td>10.7</td>
<td>10.7</td>
<td>9.4</td>
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</tr>
<tr>
<td>Girls</td>
<td>10.5</td>
<td>10.3</td>
<td>10.4</td>
<td>9.1</td>
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</tr>
</tbody>
</table>

*Adapted from Institute of Medicine [25].*
gestation, then birthweight would have dropped, but rates of LGA would not have changed. Conversely, change over time in how gestational age was assessed would result in apparent trends in fetal growth, but would not influence birthweight. One explanation that fits the evidence would be that only babies with an upward trajectory of fetal growth are increasingly more likely to be delivered earlier. Thus, a baby that would have become LGA if allowed to stay in utero longer would be delivered earlier, resulting in both lower rates of LGA and lower birthweights over time. This rationale seems implausible, however, and does not explain increasing SGA trends.

Surveillance data are an important foundation for describing secular trends in birthweight. However, many datasets report birthweight among singletons and multiples, term and preterm infants combined. Furthermore, many report rates of macrosomia and low birthweight without information on SGA and LGA. To fully understand underlying contributors to trends in fetal growth as well as gestation duration, it is crucial that data be readily available to allow determination of fetal growth, by gestation length and plurality as well as maternal characteristics.

**Conclusion**

Babies are not increasingly being born at higher birthweights. In fact, despite the headlines and counter to trends in maternal obesity, gestational weight gain, diabetes, and smoking, babies are being born at smaller and smaller birthweights, and a decreasing proportion of babies are born macrosomic. These declines are most likely largely explained by decreases in gestation length, itself caused by obstetric interventions, especially induction of labor and to a lesser extent elective cesarean delivery. However, it appears that fetal growth is also declining, at least in some settings, independent of gestation length. Reasons for this decline are as of yet unexplained and merit further investigation. Perhaps the 1879 Guinness record for heaviest baby (23.12 pounds) will remain unbroken for some time to come.

**References**


Secular Trends in Growth

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Abstract
This essay provides a brief history of the etymology and usage of the phrase ‘secular change’ followed by a description of secular changes in height and relative leg length in childhood, adolescence, and adulthood. Both positive and negative changes are described. Possible causes are reviewed, with an emphasis on nutrition, infection and social-economic-political (SEP) environments. The case of the Maya people living in Mexico, Guatemala, and the United States is given, which shows that intergenerational changes in stature and its components – leg length and upper body length – may occur in different directions and at different rates. The deleterious consequences of rapid catch-up growth after birth have been proposed as a hypothesis to explain the 150 years of positive secular change in height of populations in the richer nations. That hypothesis is found to be an incomplete explanation. Growth changes better track the rate of change in SEP factors. Epigenetic assimilation is a new hypothesis, which focuses on those epigenetic processes regulating gene expression, metabolic function, physiology, and behavior. Epigenetic assimilation shows promise to account for plasticity and intergenerational changes in human growth and development phenotypes.

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Etymology and Usage of ‘Secular’

‘... “secular trend”. This rather curious phrase denotes both the tendency to get larger and the tendency to become more early-maturing, tendencies which are usually, though not invariably, linked’ [1, p. 116].

The above quote comes from James Tanner’s A History of the Study of Human Growth. Tanner devotes only 4 of 402 pages to the topic of secular trends. This
is as curious as the phrase itself, considering that the description and analysis of secular growth is, perhaps, the single most frequent topic of human growth research, with more than 1.4 million 'hits' via Google and 859 articles on PubMed. Few if any publications explain the origin of this 'curious phrase' as applied in human biology. So, a few words on etymology and usage are in order.

The earliest publication on secular changes in human growth seems to be by Quetelet in 1835 [2]. He explained urban/rural and European national differences in average height strictly in terms of environmental and economic determinants. As discussed below, these remain the best explanations for changes in growth over time and between groups. Other 19th and early 20th century studies follow [reviewed in 1, 3, 4], but none seem to use the word 'secular'. The first such use of the term in relation to human growth seems to be by Frank in 1935 [5], where the phrase 'secular trend' refers to changes in size and biology during the growth of the individual rather than its current usage as a change in growth of groups of people over time or generations.

A search of PubMed finds the earliest use of 'secular' is in 1880 and relates to geology [6]; a few years later astronomers use the term. This usage probably stems from the dictionary definition of secular as just once in an age, indicating a relatively long span of time. The other meaning of secular is 'worldly', pertaining to the material, non-spiritual world. As used today in human biology, these two definitions are apt because the factors influencing the secular changes in growth are related to the material conditions of life, and these conditions do act on human growth over long spans of time.

The first biological usage in PubMed is a 1927 paper on the division rates of protozoans, which show 'secular changes' over 3 years of study. The first paper I can find that clearly defines how to use the term 'secular' is an economics report by Burns in 1934 who writes, 'The secular trend of an industry's production may be considered as the persistent, underlying movement of its output over a period which is “long” in relation to the changes associated with the “business cycle”. So viewed, the secular trend is irreversible within the periods of a business cycle, though it may be reversible within longer periods. The secular trend can be represented graphically by a curve and may be given algebraic expression by a mathematical equation. . . Secular trends of production express the growth (including decadence under this term) of industries' [7, p. 31–34].

As may be seen from figure 1, with few changes this quote applies to the study of secular changes in human growth. Indeed, economic growth and human growth are correlated, and both economists and human biologists study these interrelationships [4]. Changes in growth over decades and centuries usually lag behind improvements or declines in economic productivity [8–10]. More is said about this below.

By the 1930s, human biologists had published many articles on the topic of changes in growth between generations [11–13] and between immigrant parents to the United States and their offspring [14], but there is no use of the word
Fig. 1. **a**. Secular changes in the height of four cohorts of Swedish females between 1883 and 1999. During this period, average height at age 14 increased by almost 13 cm (5 inches), and final height at age 19 increased by about 8 cm (3.2 inches). Increases in the height of Swedish males during the same time were even greater, almost 20 cm (7.8 inches) at age 14 and 16 cm (6.3 inches) at adulthood. The magnitude of the positive secular trend in Sweden is similar to that in other industrialized countries (see fig. 1b below). The inset shows that as height has increased, the age at first menstruation has decreased until about 1970 and then has stabilized. **b**. Secular trend in average stature (mean or median) of men 20–39 years of age in the Netherlands (▲) and the United States (■) between 1830 and 2002. The data points are fitted with linear regression lines.
‘secular’. It is not until 1941 that Howard Meredith [15] uses the term ‘secular changes’ and ‘secular trends’ in a study of growth of two groups of people measured a decade apart. Meredith provides a good review of the topic and concludes by writing that ‘... no one really knows the cause [of secular changes] – it is a research frontier’ [p. 37]. Today, the causes are better understood and are discussed below following an overview of the changes themselves.

Secular Changes in Childhood, Adolescence and Adulthood

For the remainder of this article, the phrase ‘secular change’ refers only to increases or decreases in the mean anthropometric values of human populations. The focus is on skeletal dimensions because body mass (fatness, muscularity) is labile to short-term (i.e. within generation) influences. Hauspie et al. [16] review the evidence for these secular changes over the past century in 17 nations, including many European countries as well as Japan, Cuba, Brazil, North America, and Taiwan. They find that on average the per-decade increase in height was ~1.3 cm in childhood, ~1.9 cm in adolescence, and ~1.0 cm in adulthood. The greatest per decade increase occurred in Japan, ~4 cm from 1950 to 1960, and the smallest increase occurred in Sweden and Norway at ~0.3 cm/decade between 1952 and 1985. Note that all of the final adult increase in stature is achieved during childhood. The increase during adolescence is greater than during childhood or adulthood because faster growth rates have been accompanied by earlier maturation. As a result, puberty and the adolescent growth spurt occur earlier and the period of growth is shorter. As indicated in figure 1a, 10-year-old girls in 1999 averaged 140 cm, a stature achieved only at 13 years of age in the 19th century. During the same period of time, the age at menarche declined by nearly three years.

Not all secular change is positive. Data from South Africa [17] demonstrate a clear decline in mean stature for Blacks from the late 19th century to 1970. These stature declines are linked to the deterioration of the social, economic, and political (SEP) environment for Blacks both prior to and during the apartheid era in South Africa. White South Africans of Dutch origin experienced an increase in mean height of 0.5 cm/decade, but this pales in comparison to that for the Dutch living in the Netherlands – 1.5 cm/decade – and measured in the same years [18]. The purpose of the apartheid policies was to guarantee economic, social and political domination of the country by the White minority. My explanation for the superior secular increase in stature of the Dutch in the Netherlands as opposed to the Dutch in South Africa is that the deterioration of living conditions for the non-White population in South Africa caused by the apartheid policies could not be confined to those ethnic groups. Of the almost 39 million citizens of South Africa in 1991, 75.2% of the population was classified as Black Africans, 8.6% were known as Coloureds, 2.6% were Asians, and
13.6% were Whites. When more than 80% of a population lives under repression and poverty, the economic and social development of the country as a whole is likely to be arrested, and even the privileged social classes will be affected. The most meaningful statistic in this regard is the infant mortality rate (IMR), which is, perhaps, the best indicator of the overall health environment for any population. In 1985, IMR in South Africa was 68/1,000 live births for Blacks and 13/1,000 for Whites [19]. By comparison, the IMR in 1987 for the Netherlands, for all ethnic groups, was only 7/1,000.

An even clearer case of the negative trends in height comes from Guatemala during the period from 1974 to 1983, a time of intense civil war and political repression. Economic decline and political unrest due to the war is associated with a significant decline in the mean stature of cross-sectional samples of 10- and 11-year-old boys and girls from families of very high, moderate, and very low socioeconomic status [20]. A general deterioration of the quality of life in Guatemala, especially the quality of nutrition and health of the entire Guatemalan population, seems to be the cause of the negative secular trend. Even the very wealthy were not spared as the environmental decline affected municipal water supply systems and led to the outbreak of cholera and other epidemic diseases.

Rate of maturation also may show a negative trend, meaning an increase in the age at puberty. There is only space here for one example from Poland, where improvements in nutrition and health status led to a decline in the age at menarche by about 4 months/decade from 1955 to 1978. In contrast, from 1978 to 1988, a time of considerable political and economic turmoil in Poland, the age at menarche increased by an average of 1.7 months/decade [4].

**Changes in Body Proportions**

Positive and negative secular changes do not affect all parts of the body equally. Stanley Garn [21] noted that there has generally been a greater increase in leg length and the size of hands, feet, faces and noses than in total stature. In Japan between 1960 and 1995, male height at age 17 years increased 5.8 cm, and 4.5 cm of this increase was due to longer leg length [22]. Between birth and puberty, the legs grow relatively faster than the upper body, a pattern called the cephalocaudal gradient in growth. We might expect leg length to be relatively longer in populations that live under more advantaged circumstances, because better nutrition and health will allow for more rapid leg growth in the early years of life [23]. Hauspie et al. [16] and Cole [24] state that relatively longer legs accounts for most of the secular increase in height of all populations. They also conclude that all of the final adult increase in stature is achieved by childhood, with Cole stating that this occurs by age 2 years. Later in this chapter, we will see that these observations are usually, but not always, true.
Possible and Likely Causes of Secular Changes

Many plausible and fanciful proposals exist to explain secular changes. A few of these are transportation technology such as bicycles and railroads leading to genetic hybrid vigor as people from formally isolated villages met and married, changing climate and seasonal effects, the availability and price of sugar or other commodities as a cheap form of food energy, environmental toxicants and endocrine disruptors, such as PCBs, which may accelerate puberty, and the development of public utilities to provide heating and artificial lighting. It is also proposed that psychosocial changes in the family, in schools, via media, etc. expose ever-younger children to sexual stimulants that accelerate growth and maturation. Each of these changes may play some small role, but it is now well accepted that modifications of the SEP environment leading to transformations in the quality of life are the principle causes of secular changes of growth status. The quality of life may be measured by SEP variables such as education and literacy levels, food availability/market prices, cost of living, real wages, gross domestic product (GDP), social class and gender stratification/discrimination, rules for voting participation, and public expenditures on health. No matter which measures are used, human height is almost always greater in those populations that have more, and a more equal distribution, of these factors. The causal relationship between better SEP environments and greater mean stature is so strong that mean stature itself is used to characterize the SEP environments of historic and prehistoric populations before the invention of statistics such as GDP, literacy rates, or cost of living indices [1, 4, 8–10].

Pioneering researchers such as Franz Boas and others cited above emphasized the importance of the SEP environment as the cause of secular changes, but could at best only correlate relationships. The first paper to test the SEP hypothesis was by Acheson and Fowler [25]. They studied lower and moderate-income parents and their children, ages 2–14 years old from South Wales and upper income London families, all sampled in 1960–1961. The Welsh families formed two groups: low-income coal miners and moderate-income shop owners and professionals. Current skeletal age was assessed for each child and an adult height predicted. ‘The Welsh parents, for some or all of their childhood, were exposed to the privations of the economic depression of 1930s, but their children were born in more prosperous times since 1945. In contrast, the parents in the London sample did not suffer unduly in the late 1920s and 1930s and their children too enjoyed relative prosperity. Our working hypothesis was, then, that the between-generation difference in stature in the Welsh group should be greater than that in the Londoners’ [p. 25].

This paper is quite ‘modern’ in terms of statistical analysis and interpretation of findings. The authors found that within generations and for both sexes, mean heights declined in a linear and statistically significant manner from upper income Londoners, to moderate- and then low-income Welsh. London boys grew...
more, faster, and showed more rapid skeletal maturation than the Welsh boys (no such effects for the girls). Between the generations, the children of Welsh miners grew more (about 1 cm) than the other two groups, which supports the authors’ hypothesis. The authors consider and reject alternative hypotheses that the mean height of each group reflects genetic or ‘racial’ influences. They conclude that findings reflect the SEP environments of the two generations.

Acheson and Fowler’s conclusions are amply supported by work from around the world. The Swedish data shown in figure 1a may be explained almost entirely via improvements in public health (drinking water, sanitation), food policies, and social welfare policies. On a global basis, Hauspie et al. [16] emphasize the importance of SEP factors by writing that, ‘The secular trend in attained height and in the tempo of growth is usually more pronounced in children from low socioeconomic backgrounds, in those with poorly educated parents or in those from rural areas. More marked secular changes appear to occur in the lower height centiles. . . ’ [p. 20]. These are the groups who are most vulnerable to SEP effects as they are at the margins of society. Two especially valuable recent books, written or edited by economists, concentrate on ‘The Changing Body’ in Europe and the United States [10] and on living standards and height in Latin America [26].

In addition, there is mounting evidence that the ecology of infectious disease also plays an important role. Crimmins and Finch [27] write that, ‘If infections occur during development, substantial energy is reallocated at the expense of growth, as required by the body for immune defense reactions and for repair’. Crimmins and Finch demonstrate this trade-off between growth and host defense with 18th and 19th century data on mortality and adult stature from Sweden, France, England, and Switzerland. Declines over time in old-age mortality and increases in height, they hypothesize, were both promoted by a reduced burden of infectious disease in infancy and childhood. Part of that reduction comes from the co-evolution of diminished disease virulence and better host resistance. Part comes from SEP factors, including better public health and medical infrastructure to treat or prevent illness. A case for support of their hypothesis is the analysis of the lingering effects of the 1918 influenza pandemic. ‘Adult height [of United States men] at World War II enlistment was lower for the 1919 birth cohort than for those born in adjacent years. . . ’ [28, p. 26]. The reason for this appears to be maternal exposure to influenza in 1918, even if relatively uncomplicated, leading to pre- and postnatal trade-offs in growth of their offspring.

**The Case of the Maya**

The influence of SEP factors on the growth of the Maya people is the focus of my research group. The Maya are the largest Native American population with an estimated 7–8 million Maya living in southern Mexico and Central America.
The majority, about 6.5 million, live in the highlands of Guatemala. The living Maya are the biological and cultural descendants of the people inhabiting the same culture area prior to European contact in the year 1500 CE. Due to the SEP environment since the 1970s, including Civil War in Guatemala and social unrest in southern Mexico, an estimated one million Maya migrants live in the United States [29]. Presented here are data on the total height, sitting height, and relative leg length (RLL – proportion of stature due to leg length) of three Maya samples of boys and girls aged 4–9 years old from: (1) rural villages in Guatemala living under adverse conditions, (2) urban families from Merida, Yucatan, Mexico of the lowest socioeconomic status in Merida, and (3) migrant parents to the United States, virtually all children born in the USA [4, 29, 30].

These three samples are compared in figure 2. Their heights and sitting heights conform to expectations, in that the Maya born and living in the USA have the largest values, followed by the Merida sample and then the rural Guatemala sample. RLL does not follow the same pattern. The rural Guatemala sample has, as expected, the relatively shortest legs, but the Merida sample has the relatively longest legs, with the USA sample about midway between the other two groups. These data show that secular changes are not always due to relatively longer legs. The USA Maya are taller and have relatively greater upper body length compared with the Merida Maya.

We have a working hypothesis to explain the difference in body proportions. Guatemalan Maya have the highest prevalence of stunting (height < −2 z scores) of any population in the world. Poverty, racism, political oppression and many other SEP factors account for this [29]. In addition, the highland Maya of Guatemala live in a region of iodine deficiency which is known to reduce both stature and, especially, RLL because its effect is strongest from birth to puberty. The Merida Maya are not iodine deficient because the Mexican government requires all consumable salt to be iodized. The effect of iodine may account for 1 z score unit or more of the difference in RLL between Guatemala and Merida. The USA-living Maya children have much improved SEP conditions and are likely to be sufficient in iodine. Their parents, however, grew up in rural Guatemala, suffered iodine deficiency, and this may have had lasting epigenetic and metabolic effects, especially on the mothers, and intergenerational effects on their offspring.

Is Adult Height Determined by the Age of 2 Years?

The conclusion by some researchers that virtually all of the secular adult height difference occurs by age 2 years warrants further investigation. There are related suggestions in the literature that height stunting is both established and irreversible by about 2 years of age. If these claims are true, then there is little value in
any intervention or treatment of growth faltering after infancy and very early childhood. Our previous research in Guatemala indicates that this claim is not always true. We find that the differences in final height between girls from low-income Maya families and non-Maya girls from high-income families are due to about a 6.5-cm deficit in height at puberty (123.2 vs. 129.7 cm) and 11.2-cm deficit in adulthood (151.8 vs. 163.0) [31]. These findings indicate that interventions to improve growth for the Maya could be of benefit during later childhood and adolescence.

A new analysis carried out for this essay compares the differences in mean stature by age between the 1950s and the 1990s cohorts of boys and girls attending the American School of Guatemala. This is a private school charging a high fee, which assures that virtually all the students are from high-income families. The results are shown in figure 3 for boys and for girls. The secular change in average height tends to increase with chronological age, especially for the boys. The increases in height are not due to maturational effects as the 1950s cohort has greater skeletal age estimates than the 1990s cohort. These two analyses of Guatemalan boys and girls provide counterexamples to the claims that stunting and secular changes in adult height occur by age 2 years.

**Fig. 2.** Z scores (standardized values) for height, sitting height, and RLL for three samples of Maya boys and girls, ages 4–9 years old. The 0.0 line is the median value (50th percentile) of the Comprehensive Growth References of Frisancho [35]. Larger values indicate greater height, sitting height, or relatively longer legs in proportion to total stature. The symbols represent the mean z score value, and the error bars indicate the 95% confidence limits for these means.
It may take 150 years, or six generations, for average heights to recover following relief from nutritional, disease, and SEP adversity. Why this intergenerational inertia and why not a single-generation gain to maximum adult size? Cole’s review concludes that the intergenerational inertia is due to biological constraints, especially those related to the cost of too rapid catch-up [24]. Cole cites research on the adverse metabolic consequences (e.g. insulin resistance, obesity) of small body size at birth followed by above-average weight gain in the first year after birth [reviewed in 32]. To avoid these costs, the growth increment of each generation is constrained.

This is a stimulating proposal, but it is based on research relating to low birthweight and small birth length. Even Cole notes that, ‘Length at birth has shown no secular trend and similarly the evidence of a trend in birthweight is not strong’ [p. 165]. Positive and negative secular differences develop mostly after birth, especially during infancy and childhood [4, 10, 16, 17, 21, 22, 29].

Secular changes are better associated with, and lag behind, the slow pace of SEP changes. Rather than the consequences of too rapid catch-up growth, it is more likely that SEP factors set the pace of intergenerational secular changes.

**Fig. 3.** Change in mean stature between the 1950s and the 1990s cohorts of boys and girls attending the American School of Guatemala. Sample sizes by age group for the 1950s average 96 and for the 1990s average 150.
in growth. This may work through epigenetic growth regulators. Acheson and Fowler mention the theoretical biology of Waddington [33]. Waddington invented the term ‘epigenetic’ to describe all aspects of the growth and development of organisms above the level of the DNA sequence inherited from parents. Epigeneticists today study the regulation of development from DNA marks of methylation and histone modification, to chromosomal imprinting, to the biologocial ecology of individuals and communities, and all of the complex interactions in between [34]. Epigenetic marks on DNA were once thought to be erased at mitosis, but evidence is accumulating for their transgenerational inheritance. Waddington wrote of ‘genetic assimilation’, but it may be more accurate to use the phrase ‘epigenetic assimilation’ to explain secular changes. There are many biological examples of extreme environments producing mutant phenotypes within one generation, but several generations of ‘normal’ environments to return to the wild phenotype [34]. This may be due to epigenetic assimilation of the environment into the phenotype, which may be defined as the intergenerational persistence of epigenetic marks and processes that regulate development. Extreme environments for people include chronic malnutrition, infectious disease, racism, and poverty. Once exposed to these, people may quickly develop a phenotype of reduced body size and slower maturation, but take four or more generations to return to their original size and shape. The next phase of secular growth research will likely test epigenetic assimilation hypotheses for intergenerational change.

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Discussion on Human Biology in Motion

Human biology is not static. It changes under the influence of changing environments. Beneath the surface, there are several layers of change, overlapping, co-occurring, and blending, driven by several different mechanisms. We have names for these various layers and mechanisms: norms of reaction, developmental plasticity, acclimation, secular change, adaptation. They vary in the time required to effect a change, the reversibility of that change, and the level (e.g. individual phenotype, population distribution) at which the change is expressed. Traditionally, these domains of biological change have been studied by scientists from different disciplines: population genetics, developmental biology, environmental physiology. Only in recent decades have serious efforts been made to bridge these disciplinary divides, to form a new, integrated approach to biological change, and to apply that approach to issues in human health and disease [1].

The fact that human biology, like the biology of any other organism, exhibits change should not be remarkable in itself. But it is a concept that does not integrate well with the conceptual framework of clinical medicine and public health. Medical science often lays undue stress on the notion of homeostasis, or the resistance to change, as a central principle of human biology. Significant deviation from established norms is usually viewed as a failure of homeostasis and a hallmark of pathology. Human biology that changes non-pathologically in response to environmental challenges of different type and temporal grain challenges the very concept of norms and standards [2]. Debate and confusion can result. A particularly evident and long-standing example is the debate over growth standards [3, 4]. On one side of the debate are those who think in terms of genetically endowed ‘growth potential’ that can be limited by adverse environments to the detriment of the health of the individual and the community. On the other side of the debate are those who think in terms of optimal growth in a specific environment. The latter group tends to view human biology in terms of norms of reaction, relationships of phenotype to environment that have been produced by natural selection operating over millennia. The former group tends to view the same norms of reaction as environmental constraints on theoretical
genetic potential. The debate between these two poles has been going on for at least half a century, and has been fanned into new life by the development of the new WHO growth standards, a topic considered later in this volume.

The papers in this section focus on changes in human growth along different time scales, and consider the implications of those changes for human health. Dr. Gluckman takes the longest view, considering the way in which human developmental trajectories have evolved. Drawing on life history theory, a branch of evolutionary biology that is concerned with the coevolution of mortality, fertility, and development, Dr. Gluckman notes that many features of human life histories are derived rather than ancestral, products of our formative evolutionary history since our last common ancestor with the African great apes. Chief among these are our long juvenile period, rapid reproductive rate when adult, and extended, postreproductive lifespan. None of these aspects of human biology is fixed, however, and all show considerable environmental variation. Dr. Gluckman draws attention to the changes in rate of maturation in the past two centuries, with declines in average age at puberty of 25–30%. These changes were historically manifest in Europe and North America beginning in the late 19th and early 20th centuries, but have since been widely reported throughout the world [5]. Dr. Gluckman argues that this process of biological change has uncoupled puberty, or biological maturation, from adolescence, or social maturation, with a resulting discordance between physical and social adulthood.

An interesting question provoked by this argument is whether cognitive development, including the development of social cognition, shifts when physical development shifts. Some aspects of brain maturation appear to be tied to changing hormonal milieu resulting from adrenarche and gonadarche, suggesting a linkage between physical, reproductive, and cognitive development. However, brain and cognitive maturation also depend critically on environmental inputs, including social context and experience. These may or may not keep pace with changing conditions affecting physical development. It is fascinating to reflect that many of the longitudinal growth studies of the early 20th century, particularly in the US, were motivated by questions like these and their implications for educational and social policy.

Dr. Oken focuses on a different dimension of changing human growth, an apparent shift to a lower modal birthweight in the US and other countries over the past two decades, reversing a longer, previous trend toward increasing birthweight and increasing rates of macrosomia. While some of the recent trend can be attributed to apparent reductions in gestation length and increases in the rate of preterm births, there is a suggestion that fetal growth rates have also declined.

Dr. Oken’s presentation provokes questions about the assessment of gestational age. As ultrasound assessments become more sophisticated and widespread, a shift away from standards based on last menstrual period dating to standards based on fetal size may potentially be confounded with observed trends. Furthermore, the precision of gestational age estimates by any method
Discussion on Human Biology in Motion 129

may be much poorer than the magnitude of change in gestation lengths that have been reported.

Taking the data at face value, however, there are a number of possible mechanisms that could be at work. Changes in obstetrical practice and maternal health that are contemporary with the observed declines in birthweight, fetal growth, and gestation length are immediate suspects. But it is also possible that changes in fetal biology observed at one point in time can result from changes in obstetric and neonatal practice at an earlier period. In particular, improvements in neonatal medicine have dramatically increased the survival rate of premature and small for gestational age infants during the last quarter of the 20th century. There is evidence that infants who are small for dates or premature grow up to give birth to offspring that are also small and with shorter gestation lengths [6, 7]. Thus, the phenomenon of a trend toward lower birthweight may be a result of medical selection reducing mortality at the lower tail of the birthweight distribution.

Dr. Bogin focuses on secular changes in postnatal growth that have been documented throughout the world. The predominant pattern that is commonly observed is an increase in height-for-age, an increase in the magnitude of the adolescent growth spurt, and a decrease in the age at puberty as populations modernize [5]. Dr. Bogin notes, however, that different components of height, such as leg and trunk length, can change over time at different rates, and that trends can reverse if prevailing socioeconomic conditions regress. The proximate environmental causes of secular change in postnatal growth are several, including changes in nutrition and disease burden. The biological pathways mediating secular change in postnatal growth are also several, including acute effects during childhood and adolescence as well as changes in the early programming of developmental trajectories. It is very likely that changes co-occur at several of these levels. Environments that cause acute acceleration of growth may simultaneously stimulate shifts in programmed developmental trajectories, a process Dr. Bogin refers to as epigenetic assimilation. Both of these processes in turn may be accompanied by natural selection for genotypes with shifted norms of reaction, or what Waddington [8, 9] called genetic assimilation. The more persistent the environmental changes driving biological change, the deeper these processes of assimilation can be expected to reach.

Dr. Bogin notes that the closest correlates of secular change in postnatal growth are prevailing socio-economic-political conditions. He suggests, therefore, that patterns of human growth be interpreted as reflections of social justice. An argument of this kind fits nicely with the notion, referred to above, of genetically endowed potential for growth that can be more or less fully achieved and more or less constrained by environmental and social circumstances. However, it is a perspective that discounts evidence of trade-offs between different domains of human biology and health. Dr. Gluckman's presentation previously drew attention to the potential mismatch between physical and social maturity that can occur as a result of secular trends in postnatal growth. There is reason to suspect
that secular trends toward greater size and earlier maturation may also be associated with increased risk of deleterious conditions ranging from myopia to numerous cancers.

All three papers in this section provide evidence of the changeability of human growth patterns. From the perspective of evolutionary biology, this degree of phenotypic flexibility argues forcefully against the idea of universal norms or standards for human growth. If there were a pattern of growth that was optimal in all environmental contexts, it should be highly canalized, protected by strong homeostatic mechanisms against destabilizing external influences. In contrast, what we observe are consistent norms of reaction governing the relationship of growth phenotype to environment, something that only makes sense if human growth has been shaped by natural selection to respond facultatively to both acute and chronic environmental conditions. Those genotypes that have allowed for such flexibility have survived to shape our biology rather than genotypes with rigid homeostatic control. If this is the correct view, then it makes no sense to ask, ‘How should humans grow?’ Rather, it only makes sense to ask, ‘How should humans grow under such and such a set of environmental conditions?’ To adopt a universal set of growth standards, such as those proposed by the WHO, would only make sense if we are to accept the notion of a single, ideal environmental context for all humans to inhabit.

If medical science and medical practice is to be based on a modern understanding of human biology, it must, as Dr. Gluckman and others have argued, incorporate principles of evolutionary biology. With those principles in place, changes in human biology will no longer be a mystery, but a revelation.

Peter T. Ellison

References

Economic Drivers and Consequences of Stunting

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Abstract
This paper reviews evidence addressing four questions pertinent to the understanding of the economic returns to investing in nutrition: (a) Where are the promising areas of interface between economics and nutrition? (b) What is the contribution of income growth to improving nutrition? (c) Is adult chronic disease being given too little consideration in nutrition programs? (d) More generally, are we using the right outcome measures to assess nutrition interventions?

Introduction

A recent World Bank publication concluded that it would require USD 10.3 billion of public funds annually along with USD 1.5 billion household investment in nutrition to implement a package of thirteen proven nutrition interventions in the 36 countries that contain 90% of the world’s malnourished children [1]. This clearly is not a large investment on a global scale, even in the current climate of fiscal austerity; the estimated costs amount to USD 28 per malnourished child. What might be expected as the outcome of this investment?

While the costing study was not intended to delve into this question, other papers have attempted to assess the economic returns from nutrition programs. Two such studies were designed to compare the economic benefits relative to the program costs with other investments outside the health sector using a common
methodology [2, 3]. Two panels of independent reviewers, the majority of whom had received a Nobel Prize in economics, ranked nutrition investments at having amongst the highest economic returns in successive reviews called the Copenhagen Consensus 2004 and 2008. Implicitly, then, these economists accepted the evidence base presented for these studies and the assumptions underlying the calculations, such as how to compare future gains against current costs.

The body of evidence and the challenges for making robust estimates are reviewed elsewhere [2–4]. Some improvements in nutrition are sufficiently widely distributed that their contribution to economic growth can be shown in the aggregate. For example, much of the economic growth in Europe from the 1800s has been attributed to improved nutrition, mainly via food availability [5]. Still, the bulk of the evidence for the benefits of many of the interventions comes from randomized trials which provide the effect size of an intervention on mortality, physical growth or cognitive capacity. The effect sizes were then linked to what is known about the contribution of either stature or cognitive development and schooling to derive the impact on productivity over a lifetime. Additional evidence comes from trials that track an intervention in childhood through schooling [6, 7], and to their adult earnings [8]. These longitudinal studies support the larger body of indirect evidence. While these studies find savings from reduced health expenditures over a lifetime, productivity gains dominate the total benefits from nutrition interventions.

A new study from Indonesia presents economic returns looking at the delivery of a package of services at scale rather than an intervention-specific impact evaluation. This study estimated the economic rate of return – the point at which discounted future earnings would just offset the costs – to be over 13% [Qureshy, unpubl. data]. As this is larger than the 3 and 6% discount rate used in the Copenhagen Consensus studies, it would also generate a highly favorable benefit:cost ratio at the discount rates used with the methodology employed for the consensus comparisons.

As with any field of study, new trials will help refine these economic calculations. Horton et al. [3] found sufficient new evidence on deworming and zinc fortification to update benefit:cost estimates from Behrman et al. [2]. A proposed update for 2012 might add a benefit:cost assessment of community treatment of acute malnutrition as well as the global experience on folate fortification. However, rather than reviewing new evidence on specific interventions, the present paper will reflect on four overlapping themes that go towards the questions that economists should be asking in order to contribute to health policy more effectively. These are:

a. Where are the promising areas of interface between economics and nutrition?
b. What is the contribution of income growth to improving nutrition?
c. Is adult chronic disease being given too little consideration in nutrition programs?
More generally, are we using the right outcomes measures to assess nutrition interventions?

**Areas of Synergy between Economics and Nutrition**

Most health trials, particularly discrete dose-response studies of micronutrients and deworming, are grounded in a physiological model, one that can be tested in a laboratory. Still, this advantage pertains more to efficacy studies than efficiency studies. The latter are driven in part by the nature of demand; one needs to understand the decisions made by heterogeneous households in order to move from the measurement of the impact of a treatment on the treated to one that assesses the impact on a population [9]. One also needs to understand how the delivery is structured and how both service providers and communities respond to incentives. The need to understand consumer demand and programs to stimulate service utilization has prompted a spate of studies of programs designed to encourage households to attend clinics or participate in other health services such as conditional cash transfers (CCTs) [10]. Similarly, trials are underway in a variety of settings to learn more about result-based financing and other incentives to improve performance [11].

An improved understanding of consumer demand and provider incentives will help bridge the gap between efficacy trials and economic efficiency results. Generally, however, few studies include the data on delivery costs necessary to fully understand the economic returns. This has a particular bearing on program heterogeneity. The physiology of the response of, say, a child in a remote mountain village to a health intervention may differ little from that of a child in the capital city; the costs of providing the intervention, however, may differ by an order of magnitude. Moreover, the full economic costs of an intervention differ from the nominal costs of providing a service due to a variety of factors such as the opportunity cost of time for households as well as staff and the costs of raising revenue. A full accounting will include such costs.

Even when an evaluation addresses the distribution of benefits within a population, it is difficult to place a value on one of the key outputs of many programs, an increase in the equity of opportunity. Similarly, programs that transfer income or food in order to increase demand for health care may be able to measure the impact on services and outcomes and even to estimate the economic value of these outcomes; yet, because they cannot fully value the transfer itself, they underestimate the total impact. Most will agree that transferring a dollar from the average consumer to the poorest raises welfare. However, the value in a benefit:cost ratio is not the transfer itself but only the difference between how much the society values this consumption by the target population over the average. Thus, quantifying these benefits is tricky. However, if this is not done, then a major role of a demand side intervention in nutrition is missing and the overall program will
appear less beneficial than it actually is. That is, if the question is whether a CCT or similar program is the best way to invest in nutrition in a certain environment, the answer under criteria of health impacts alone may be no. If, however, the question is whether the joint benefits from a CCT provide the best way to spend a transfer budget, the answer in that same environment may be quite different. Economic tools can be applied to such questions, albeit with challenges.

**Role of Income Growth in Addressing Nutrition**

Within most countries as well as comparing between countries, income growth even when evenly distributed over a population has a relatively modest, although significantly positive, impact on undernutrition rates [12]. There is little dispute on this point, and on the converse proposition that reducing malnutrition promotes income growth. The empirical magnitude of the evidence, however, argues that since there is not a sharp gradient of improved nutritional status as one moves away from poverty, there is a need to pay greater attention to specific programs that improve nutrition than might be the case if economic growth by itself achieved these gains.

To illustrate, in the 1990s India experienced a growth rate in GDP per capita of 5.3%, while malnutrition declined by only 1.5% [13]. This is lower than the 2.5% expected from global patterns and the rate of income growth that India achieved. But, unfortunately, relatively few low-income countries have sustained economic growth as large as India’s recent progress. Thus, relatively few countries have been able to rapidly drive down malnutrition on the basis of economic growth alone.

Households can be ranked by indices of wealth available in demographic health surveys. Table 1 reports rates of underweight children by such rankings. Using these data, one can project the national average rates of underweight children if the poorest 40% in any country were to have the characteristics of the middle quintile. For example, were all households in the lowest two quintiles by wealth in Pakistan to have the characteristics of the middle quintile, poverty in the country would be virtually eliminated, yet over 38% of the entire population of children would still be malnourished. Taken at face value, the data from Ethiopia and Rwanda imply that giving the quintile with the fewest assets the characteristics of the middle quintile would actually increase malnutrition in the country.

Such evidence underlines the view that although income growth is associated with lower rates of malnutrition, that association is not strong enough to expect growth alone to make specific investments in nutrition redundant. That is, investments in the overall economic climate do not fully substitute for investments in nutrition. But there is another linkage between economic growth and expected returns to nutrition investments that can be illustrated with a simulation based on Alderman and Behrman [14].
That study of the economic benefits from reducing low birthweight assumed that productivity gains are proportional to earnings and, further, that these are constant over the lifetime of the worker. If, as is more plausible, the productivity of workers increases over time as other complementary investments are made, this assumption would underestimate the contribution of investments made in human capital. Suppose, for example, there is an average productivity growth in the economy of 2% per annum, the economic benefits of preventing one low-weight birth in the base model presented in Alderman and Behrman would increase from USD 510 to 783. The benefits from reduced non-communicable diseases (NCDs) would also increase in absolute and relative terms with assumed higher growth of productivity since the cost of NCDs includes the costs of lost earnings. This illustrates that higher rates of income growth are complementary to investments in child capacity. As higher economic growth rates do not increase the cost of the initial investments, at any given level of development the economic returns from investments in nutrition are actually higher in a dynamic economy than in a stagnant one.

**Some Implications of the Double Burden of Malnutrition**

It is regularly pointed out that despite impressive economic growth India has the largest number of malnourished children in the world. It also has the largest number of people with diabetes despite moderate levels of obesity [15].

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**Table 1. Nutrition and poverty: prevalence of child underweight by wealth quintiles**

<table>
<thead>
<tr>
<th>Region</th>
<th>Country</th>
<th>Lowest</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>Highest</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Asia</td>
<td>Bangladesh</td>
<td>59</td>
<td>53</td>
<td>45</td>
<td>43</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>India</td>
<td>61</td>
<td>54</td>
<td>49</td>
<td>39</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Pakistan</td>
<td>54</td>
<td>47</td>
<td>43</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td>Africa</td>
<td>Benin</td>
<td>29</td>
<td>30</td>
<td>23</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Burkina Faso</td>
<td>42</td>
<td>40</td>
<td>41</td>
<td>39</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Ethiopia</td>
<td>49</td>
<td>51</td>
<td>51</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Mozambique</td>
<td>31</td>
<td>28</td>
<td>26</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Rwanda</td>
<td>27</td>
<td>30</td>
<td>28</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Tanzania</td>
<td>25</td>
<td>26</td>
<td>22</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Uganda</td>
<td>27</td>
<td>26</td>
<td>25</td>
<td>19</td>
<td>12</td>
</tr>
</tbody>
</table>

Data for children <5 years old; below –2 SD. Source: Gwatkin et al. [32].
These two statistics may have a common origin, one that is in the structure of fetal development. Gluckman et al. [16] pose basic and applied research priorities that address this linkage and which come out of new perspectives of developmental plasticity. These include questions such as what level of risk in later life disease is acceptable and what are the benefit:cost ratios of early interventions.

Another simulation based on Alderman and Behrman [14] is germane to these questions. In this experiment, the costs of NCDs attributable to a reduction of low birthweight are varied by assuming that they are centered at age 49 rather than 60. However, because future benefits are discounted relative to current benefits, the contribution to total estimated benefits – based on the odds ratio of chronic disease for low birthweight children and an assumed cost equivalent to 10 years’ earnings from lost income plus medical care for those with NCDs – is still small. The benefits increase from USD 15 in the initial paper to USD 32 under the new assumption. These would be 6% of the new total. The proportional increase is larger at higher discount rates than the 5% used in this simulation, but from a smaller base.

An analogous experiment using the data from Indonesia has a similar outcome. In this case, the economic rate of return rises modestly from 13.02 to 13.11. To be sure, these two illustrations do not cover the full range of links between malnutrition and NCDs. Moreover, the assumed costs for the treatment of NCDs may be the weak link in the simulation. Early onset of diabetes and other chronic illnesses may not only change the timing of costs, it may change the number of years of the direct treatment costs as well as the total indirect costs of reduced productivity. Adolescent diabetes may have different risk factors than adult onset and different costs for treatment. Zeroing in on these costs is likely a promising area for future research.

However, the simulations also confirm that under standard methodologies for estimating benefits and costs of interventions, the timing of NCDs is not a major determinant of the economic benefits for investments in children. The benefits are still dominated by enhanced cognitive ability and increased schooling. Advocating improved maternal nutrition as a means to prevent NCDs, however, reinforces rather than diverts attention from the priority focus for early childhood education in the earliest years in a child’s life.

Recent research posits risks for obesity and associated diseases from too rapid weight gain after age 2 years [17–19]. While incorporating this knowledge into models of the overall benefits of investments in nutrition would have little impact on total returns to a package of nutrition interventions, it should have profound implications for the estimated benefits and costs of specific interventions such as daily feeding of children 3 or 4 years old. This issue of age targeting is tied to the issue of what indicators should be prioritized. This is discussed below.
Additional Perspective: Are We Targeting the Right Outcome?

Table 1 presents malnutrition in terms of underweight, in part because that is the indicator tracked within the Millennium Development Goals. Additionally, weight-for-age is somewhat easier to collect with accuracy in large sample surveys given the challenges for measuring recumbent length for young children. Moreover, the increased availability of digital scales that can be used to weigh a child in its mother’s arms adds to convenience and reduces rounding errors. Weight- and height-for-age move in parallel over large populations from birth until roughly 17 months and again after 24 months [20]. In the latter case, there is little movement at the population level in either indicator.

Still, weight-for-age may not track height-for-age over the ages commonly targeted in nutritional programs [21]. For example, at a program level in Chile’s supplementary feeding program, weights increased relative to international references while heights do not. This risks contributing to obesity. Chile’s program is unique in coverage, given the low levels of malnutrition in that country. This may account for the difference in the diversion of weights and heights there compared to global patterns. Moreover, while anthropometric status averaged over a population may change little after 24 months, tracking data show that catch-up growth as well as faltering continues for individuals beyond the first 2 years [22]. Still, the programmatic conclusion – that the focus should be on maternal nutrition and the 2 years immediately after a child’s birth when linear growth is most malleable – is fully consistent with the larger body of evidence.

Just as low birthweight is a convenient but imperfect indicator of the outcome of a pregnancy, underweight and stunting are limited as indicators for nutrition programs for young children. For one thing, micronutrient deficiencies do not always contribute to stunting, even if they are causally linked to both child mortality and long-term cognitive impairment. Moreover, the link between mortality and either stunting or underweight [23] is only a portion of the consequences of malnutrition and one that might be receding in importance with progress in child survival. Somewhat surprisingly, while the majority of nutrition-related deaths can be attributed to risks related to inadequate breastfeeding, or weaning, the odds ratio of mortality risk from various dimensions of malnutrition is often reported for the age 0–59 months, beyond the most critical period of mortality risk. As such, these results fail to exploit the opportunity to pinpoint the optimal timing for interventions.

Height-for-age is not only associated with risks of mortality, it is also a strong predictor of the human capital of adults [18]. A recent review confirms that nutrition strongly influences cognitive and non-cognitive skills including a range of socio-emotional behavioral factors such as conduct, motivation, persistence and adds new insights on factors such as the role of essential fatty acids.
in pregnancy and on the timing of risks [24]. The study reiterates the importance of maternal nutrition for subsequent cognitive development of the child and also confirms that timing is essential. Growth in the first 2 years is associated with cognitive development while later growth is not. Similarly, micronutrient supplementation has a much stronger impact on subsequent schooling than later supplementation. Maternal education and household assets seem to be protective factors that mitigate the negative impact of either malnutrition of other forms of stress on cognitive development. It is, however, difficult to measure the heterogeneity of risk or of program responses across socioeconomic strata. This is particularly true for the earliest lags in development that overlap with growth faltering.

At slightly older ages, however, the interaction of cognitive development and wealth is readily apparent. Figure 1 indicates that young children in Cambodia and Mozambique are exposed to large cognitive delays that increase with age. The figure also shows that cognitive development is associated with socioeconomic status as proxied by wealth and caregiver education. These gradients remain even when accounting for mediating factors such as nutrition and parenting and are documented for noncognitive as well as cognitive skills [25]. Such patterns are not limited to very poor countries as represented by Cambodia and Mozambique; similar patterns are observed for Ecuador and Turkey, both middle-income countries [26].

The failure of low-income children to develop intellectually at the same pace as children from relatively well-off households – none of the Mozambique sample can be considered well-off by any absolute measure – buttresses the argument that focusing on physical growth past the age of 2 years is the wrong action for the right motives. If the goal is to reduce inequity of opportunities, then instead of food provided for all children in this age bracket, the objective should be to provide cognitive stimulation.

Many studies use height in regressions exploring determinants of schooling or learning or, occasionally, wages. Often, these studies recognize that height is endogenous and employ appropriate statistical techniques to isolate causality. However, it is unlikely that height per se accounts for the majority of the improvement in schooling and earnings. More plausibly, height is an indicator of overall health and cognitive ability. Indeed, analysis of the data used in a long-term analysis of a nutrition intervention in Guatemala indicates that the cognitive effects of the supplementary feeding rather than its impact on physical size drive the outcomes for adults [Behrman, unpubl. data]. This holds for developed as well as developing countries [27].

Few studies, however, have the necessary data to separate out the impact of physical growth from cognitive and emotional development. It is noteworthy, however, that studies of interventions that provide both stimulation and supplementation to malnourished children 18 months or older have found that it is the former rather than the latter that helps close the gap in cognitive skills.
More generally, there is a growing body of evidence that it is possible to affect the development of children at very early ages [30]. Moreover, economists are joining nutritionists and other child development specialists in exploring economic returns of these early interventions with a particular focus on timing as well as complementary inputs necessary for achieving objectives [31].

In summary, recent evidence on the timing of health risks and that on the timing of other developmental risks point to similar conclusions. Programs need to prioritize women of child-bearing age. Moreover, they need to target nutritional interventions to children more finely than is often done and to reconsider the role of food supplements. This not only concentrates limited resources where they can be most productive, it may also reduce health risks that appear...
later in life. Even where health risks from feeding programs are not likely, a shift in an emphasis on physical growth to cognitive growth among relatively older children in non-crisis situations would rebalance efforts for stimulation and those for feeding.

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References

Discussion on Economic Drivers and Consequences of Stunting

Secular trends in growth are thought to be driven by improvements in diet and nutrition, and reduced morbidity, both of which relate to underlying social and economic factors. Dr. Alderman’s presentation brings an important economic perspective to our understanding of what drives healthy growth by considering how economic change influences child growth and development outcomes, and in turn, how early growth relates to adult human capital. This model is critical for estimating the economic returns to investments in child nutrition programs, thus informing child health policy. The presentation highlighted not only the important studies relating improved nutrition to better cognitive development and schooling, but also recent work on how faster child growth rates related to increased risk of obesity and increased risks of non-communicable diseases (NCDs) in adulthood. The latter raises the important question of evaluating ‘trade-offs’ when considering the long-term effects of early child nutrition.

The interaction of nutrition, economic factors, and health is becoming more and more complex in the context of the dual burden of undernutrition and obesity being experienced in many low- and middle-income countries around the world. While there are dramatic increases in child, adolescent and adult obesity, coexisting stunting and micronutrient deficiencies persist in the same communities, and even within the same households. From a public health perspective, there is increasing concern that some ‘solutions’ to child malnutrition may have the undesired effect of increasing risk of obesity and risk of NCD.

The discussion followed several themes in Dr. Alderman’s paper. The first addressed some of the assumptions used to estimate the rate of return from investments in child nutrition programs, especially in light of the current concerns about how faster early child growth relates to adult chronic disease. Specifically, questions were raised about which adult outcomes are considered and valued, with a focus on why the detrimental effects and costs related to the long-term effects of chronic diseases are discounted relative to the benefits of
improved cognition, attained schooling and earnings. For example, Dr. Forrester asked for a perspective on savings accrued in avoiding chronic diseases down the line versus huge budgetary expenditures on prevention or clinical care. Is early intervention almost irrelevant in terms of savings or economic value in adulthood versus the huge economic expenditures on clinical and preventive care? Dr. Alderman explained that if the money used to prevent a chronic disease 50 years down the line was invested in other things that give a higher return, this would leave more money available to the economy to address the illnesses and the lost earnings. However, this logic may not apply equally well to longer (for example, the 50–60 years to heightened chronic disease morbidity and mortality) versus shorter term returns. Thus, it is important to consider the age at which detrimental economic effects of NCDs begin to accrue. A key point is that assumptions about the discount rate will influence estimates of the benefit: cost ratio of early childhood investments. Dr. Godfrey also questioned whether discount rates take account of the fact that in many settings, health care inflation is in excess of ordinary inflation, with important implications for the costs related to NCDs in low- and middle-income countries.

The importance of early child nutrition for cognitive development and schooling relative to later risk of NCDs is a key concern for low- and middle-income countries undergoing rapid economic development. Dr. Alderman's work shows the importance for investments in early child development and nutrition, particularly in dynamic economies. A key point concerns vulnerable periods: the optimal time for improvements in linear growth and brain development is during the first 1,000 days – from conception to about 2 years of age. The economics and human growth literatures provide substantial evidence to support early childhood programs. In contrast, the literature relating infant and child weight gain to later NCD outcomes shows that faster weight gain in later childhood and into adolescence has a much larger effect on young adult obesity and NCD risk. Thus, Dr. Alderman's conclusion was that 'benefits (to early interventions) are still dominated by enhanced cognitive ability and increased schooling.' Optimization of prenatal and early child nutrition may also have the benefit of reducing a child's susceptibility to the environmental influences that increase the risk of NCD development.

The importance of age-targeting of nutrition interventions is brought into focus by the trends of increased child obesity alongside continued stunting in low- and middle-income countries around the world. For example, it has been suggested that child feeding programs for preschool and young school-aged children may be contributing to excess weight gain. This, however, may reflect the lack of targeting of programs to specific groups of at-risk children. The role of school-based feeding programs was also raised by Dr. Singh, who noted that in India, provision of midday school meals enhanced school attendance, thereby providing both food and knowledge to children. However, as noted by Dr. Alderman, school-based feeding programs have a limited ability to address
brain development, coming at an age when cognitive development has already been impaired. This emphasizes the importance of providing integrated nutrition and development interventions to young children (under 2 years), rather than focusing only on young child feeding.

Another area of discussion focused on indicators: what should we measure and monitor? The Millennium Development Goals currently focus on child weight status. Dr. Alderman’s presentation supports the monitoring of child linear growth and cognitive development – both as indicators of the success of early child nutrition programs, and as predictors of later human capital outcomes. The selection of indicators of child development was a discussion issue raised by Dr. Law, who was concerned about the potential for biased estimates of program effects if indicators such as the child development index are widely adopted. Dr. Alderman noted the potential for bias with programs ‘teach to the test’, and therefore advocated for a balance between more physical health-oriented indicators and cognitive outcome indicators.

What are the key messages for policy makers and clinicians, and what are the needs for further research?

Upon hearing that faster child growth rates increase later risk of NCDs, clinicians in resource-poor settings with high rates of child stunting and other forms of malnutrition often ask, ‘so what should we do? Should we not promote compensatory growth in small for gestational age or growth restricted infants.’ A key message for clinicians in these settings is that **optimization** of child growth and development in the first 2 years of life should be a high priority, because of the importance of this highly sensitive period for brain development. Gains to cognitive outcomes and linear growth should outweigh concerns about long-term NCD risk. At the same time, it is important to avoid overfeeding of infants and young children to prevent the development of overweight and obesity. Thus, targeting child feeding programs to those with specific needs is critical.

In the context of child nutrition programs and policies, Dr. Alderman’s presentation highlights the importance of investments in targeted nutrition and child stimulation programs early in life to achieve optimal child linear growth and brain development. Timing is important: investments in child nutrition have the best returns when made in the first 2 years of life.

At the same time, it is important to recognize that improvements in socioeconomic status in low- and middle-income countries are contributing to the development of obesity and related NCD risk, leading to a dual and very costly burden of over- and undernutrition in resource-poor settings. The future health care costs related to NCDs are likely to be overwhelming, as countries such as India and China confront the very large numbers of individuals with diseases such as type 2 diabetes. This points to the need for a better understanding of how to direct investments in early nutrition to optimize **all** outcomes: to enhance intellectual development, prevent stunting, and develop ideal body composition. Because of the complexity of pathways through which socioeconomic
status factors influence child linear growth, weight gain and disease risk, further research is needed to gain a better understanding of myriad beneficial and detrimental effects and correlates of early child growth. On the one hand, the lack of success of many nutrition supplement programs in ameliorating stunting points to the need for a greater understanding of how a full range of factors, including not only nutrition, but also gut health, inflammation, and morbidity affect child growth and development. On the other hand, a better understanding of the factors that are contributing to the early development of obesity and risk factors for NCDs is also needed. Unfortunately, we lack good information on the specific diet for infants and young children that would accomplish both of these aims. Dr. Alderman noted the importance of randomized controlled trials for answering key questions.

Finally, the presentation and discussion emphasized the importance of choosing the right indicators of child health – including a focus on linear growth in addition to early weight gain, as well as good, unbiased indicators of child cognitive development.

_Linda S. Adair_
Epidemiologic Transitions: Migration and Development of Obesity and Cardiometabolic Disease in the Developing World

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Abstract

For centuries, the challenge has been the maintenance of bodyweight in the face of marginal food availability. Since the industrial revolution, energy expenditure related to economic activity and domestic life has fallen progressively as technological innovation has replaced muscular power with labor-saving devices. This fall in activity energy expenditure however has not been associated over this entire period with population weight gain. In the 1970s and the 1980s, there was an abrupt uptick in the rate of rise of relative weight in industrialized countries followed rapidly by developing countries. This has led to high and increasing rates of overweight and obesity in high-income countries worldwide, but also an alarming inclusion of low- and middle-income populations in this obesity epidemic. The precise drivers of these concurrent epidemics are not agreed, but probably include on the one hand an increase in dietary energy intake resulting from the impact of industrialization and globalization on food availability and price. On the other, there is the facilitating underlying status of a steadily falling activity energy expenditure as muscle power as an input into economic production as well as household and leisure activities has been supplanted. The rise in population weight without accompanying linear growth manifests as obesity. The accretion of fat as well as the response to other environmental exposures during progressive industrialization and modernization has evoked an accompanying epidemic of cardiometabolic pathology that has significant impact on health as well as macroeconomics. Given the power and presumed irreversibility of industrialization and globalization, our ability to reverse these obesity epidemics is heavily dependent on new knowledge being developed which gives insight with prevention and therapeutic implications on the proximal and distal drivers of this progressive positive energy balance.
Introduction

Since the 1970s and 1980s, there has been a simultaneous rise in population weight gain, beginning first in richer industrialized countries, but rapidly also becoming evident in low- and middle-income countries [1, 2]. When quantified in 2004, almost 1.8 billion people globally were overweight (body mass index, BMI >25) and approximately 500 million, obese (BMI >30) [1]. Indications are that the epidemic will continue to grow in size insofar as about 170 million children (<18 years) are either overweight or obese [3]. Overweight tracks, so that on average, fat children become fat adults, and herein lies a glimpse of the future, absent successful intervention.

Obesity is associated causally in some instances, comorbidly in others, with a group of non-communicable diseases (NCDs) including hypertension, diabetes, stroke, coronary artery disease and cancers of breast, colon, and prostate [4–6]. Obesity and its comorbidities were calculated in 2004 to account for 36 million disability-adjusted life-years and the health service costs attributable to obesity amounted to up to 6% of total spend [5, 7]. The NCDs are also the leading causes of mortality, globally, and the projections are for a continued rise pari passu with the continued evolution of the obesity epidemics.

The specific determinants of sustained weight gain leading to obesity in most populations worldwide remain unknown despite a clear understanding of the theoretical basis of energy balance [8]. Sustained population weight gain appears to take place when populations adopt a capitalist or industrial style economy, and this is presumed to change the environments in myriad dimensions including wealth accumulation, the contingent allocation of disposable income on goods and services that affect energy balance both proximally and distally, alteration in the quality, quantity, price and availability of foods, and uptake of energy-saving technologies into the economy as well as into the domestic space [8]. The final common pathway is a positive energy balance, an accumulation of the excess calories when intake exceeds expenditure, whether due to an increase in energy intake, reduction in physical activity energy expenditure, or both, to varying degrees [9–11].

Poorer countries bear the brunt of the epidemic of NCDs, a counterfactual but unfortunately accurate assessment, for while prevalence rates might be higher in many high-income countries, the rate-population product places the major burden squarely in the low- and middle-income countries [1, 5, 12]. There is also a fear that as these previously undernourished or marginally nourished poor populations accumulate wealth, the magnitude of their response to the obesogenic influences that accompany that increase in per capita GDP will exceed those experienced in richer populations. Thus, it has been proposed that exposure to undernutrition in early life, and intergenerational undernutrition modifies the susceptibility to become obese and develop a comorbid NCD. This is because undernutrition in pregnancy is now recognized to affect
the metabolic and physiological equilibrium set points and adaptive capacities of the child, and later, adult offspring through epigenetic mechanisms which increase susceptibility to obesity and the cardiometabolic diseases [13–15]. Such mechanisms give rise to phenotypes that are characterized by capacities that are constrained metabolically and physiologically and set points that are inappropriate in relation to demands that exist in our current globalized economies. Thus, when such individuals and populations come to operate in environments where the chronic obesogenic exposures place demands on systems that exceed their programmed capacities, they are metabolically and physiologically overwhelmed resulting in dysfunction that manifests as obesity and its comorbidities. This scenario in which pregnancy undernutrition developmentally entrains individuals to fit a nutritionally deprived environment, but such individuals come to live in obesogenic environments is most obviously evident in countries with a history of intergenerational undernutrition such as India, China, Latin America and sub-Saharan Africa. Here, for convenience we will emphasize the experience among African origin peoples with obesity and cardiometabolic comorbidities as an example, but the principles are equally applicable to all previously poor and marginally nourished populations.

**Obesity and Comorbidities**

There is evidence that worldwide the rate of population weight gain is high. For some populations where there are longitudinal data available on weight and height, it has been shown that the trajectory of adiposity has become steeper in the last two decades of the 20th century [2]. Thus, in the United States, an abrupt inflexion in the annual rate of rise of BMI was noted in 1985 [16]. The cause remains to be explained as there were no recorded similarly abrupt associated changes in dietary intake patterns or physical activity. Norway demonstrated a similar phenomenon in 1995 [17]. Among African populations, there is also evidence of an uneven secular trend in population weight gain, but overall trend data are scarce [11, 18]. Thus, the phenomenon of increasing obesity is global, but there is evidence that the trajectory of increase is higher in countries that have previously been poor. However, population trend data are not widely available across the different stages of economic development, and thus the validity and generalizability of this observation and the underlying explanations are unknown.

Between the 16th and 19th centuries, some 15 million people from Western Sub-Saharan Africa experienced forced migration to the Caribbean and the United States. Today, the contemporaneous existence of genetically related populations living in three settings that are at distinctly different stages on the economic development scale (low income, West Africa; low middle income, Jamaica and high income, United States) creates a context where ecologic comparisons of the impact of socioeconomic environment on health are possible.
These contrasts are made possible by the natural migration experiment; there is compression in the time dimension, allowing the evolution of the socioeconomic impact on a single population to be imputed by cross-sectional comparisons of populations captured at different stages of the process. These migrant populations suffered significant social and economic disparities as slaves then; social inequalities still persist centuries later, and within country, it is unsurprising, given knowledge of the drivers of inequalities in health, that these populations experience higher rates of obesity and comorbid hypertension, diabetes and atherosclerotic vascular disease [20]. At the ecologic level, what is observed is a gradient of obesity and related disorders, rural to urban in country, as well as a gradient by country trans-Atlantic, West Africa through the Caribbean and into the United States [20–23]. Thus, populations living in sub-Saharan Africa today like in many other low- and low- to middle-income countries, show higher rates of obesity in urban populations compared to those rural (fig. 1) [24]. Compared to derived populations in the Caribbean, these ancestral populations from West Africa have lower relative weight (BMI) and percent fat, and African-Americans have the highest rates of overweight and obesity of the three groups of populations. Hypertension rates are also lowest in West-African populations, and there is a positive gradient of prevalence rates as populations traverse the nutrition and epidemiologic transitions with African-Americans displaying the highest rates (fig. 2, 3) [19]. This is also true for diabetes (fig. 4) [21]. Although stroke and myocardial infarction have not been evaluated in this manner in these populations, the risk markers for these atherosclerotic sequelae are also present in all these populations and also demonstrate a gradient in level, east to west. Lastly, the relevance of economic advancement and its coincident social and cultural changes are seen in the strong positive association of obesity and its comorbid cardiometabolic diseases with the per capita GDP (fig. 5).
**Fig. 2.** Prevalence of hypertension in populations of African origin living contemporaneously in West Africa, the Caribbean and the United States (International Collaborative Study of Hypertension in Blacks, 1995). Hypertension defined as systolic blood pressure $\geq 140$ or diastolic blood pressure $\geq 80$ or taking hypertension medication.

**Fig. 3.** Population prevalence of hypertension and mean BMI in African-origin populations in West Africa, the Caribbean and the United States (International Collaborative Study of Hypertension in Blacks, 1995).
Energy Balance: Activity Energy Expenditure and Population Weight Gain

There are a few simple and appealingly straightforward questions regarding the relationship of activity energy expenditure to population weight, and rate of weight gain, that are unfortunately not accompanied by readily available answers. These include: (a) Is population weight gain associated with a reduction in activity energy expenditure? (b) Will small increases in activity energy expenditure to match the calculated average daily energy surplus prevent weight gain? (c) What is the role of dietary energy intake as well as pattern of dietary

Fig. 4. Prevalence of diabetes in populations of African origin living contemporaneously in West Africa, the Caribbean, the United States and UK.

Fig. 5. Relationship of hypertension risk and index of country economic status in populations of African origin living in West Africa, the Caribbean and the United States (International Collaborative Study of Hypertension in Blacks, 1995).
intake (fats and sugars consumption) on energy balance and weight gain? A wealth of theoretical propositions does exist, but unfortunately very scant and inconsistent data relevant to all these questions are available and therein lies the imperative for scaled up research in these areas [8]. Most of the information available globally is questionnaire based. Questionnaire estimates of activity energy expenditure are notoriously unreliable, and thus it is probably unsurprising that the findings relating activity energy expenditure to baseline weight and weight change on follow-up are not consistent. However, the use of doubly labeled water (DLW) to estimate energy expenditure provides much greater precision; indeed DLW is the gold standard against which other methods are used in free-living populations. Nevertheless, the data available with this precise instrument remain conflicting [9, 10, 25, 26]. Thus, the relationship of baseline activity energy expenditure with body composition is itself inconsistent. Additionally, the relationship of activity energy expenditure with weight gain on follow-up is even more inconsistent. For example, in Jamaica and Nigeria, DLW-measured activity energy expenditure has been shown in a cross-sectional analysis to be inversely associated with body fat. However, this intuitively correct association is not consistently demonstrated even when precise tools like DLW are used in other samples from the same and related populations. So too are the data relating activity energy expenditure at baseline and weight change on follow-up. This is so in circumstances for example, in which the rate of weight gain in Jamaica was large (1.4 kg/year), some three times that observed in both Nigeria and among US Blacks [11]. Longitudinal studies performed on samples drawn from these populations did not reveal a strong relationship of weight gain to baseline energy expenditure [11, 25, 26]. Perhaps this observation of inconsistent relationships between activity energy expenditure and cross-sectional and longitudinal weight change is explainable by a long-standing hypothesis that there is a minimum energy expenditure threshold of TDEE 1.7•REE, below which weight gain is predictable and inexorable; above this point, weight gain is arrested [27]. It is thus important to more fully characterize, using appropriately precise measures, the energy expenditure of populations that are at different points in the nutrition and epidemiologic transitions.

However, if we are honest, an equally obvious interpretation of these data is that in our environments, despite the existence of a historical decline in physical activity related to the removal of muscular power from industrial and agricultural production as well as domestic life, it is the dietary intake that more consistently and powerfully determines energy excess and therefore weight gain [2]. Thus, in addition to possessing tools to accurately measure energy expenditure, it is now vital to acquire similar tools for the assessment of dietary pattern and energy intake. It is equally important to measure dietary energy intake as well as aspects of the diet such as the energy density related to oil/fats and simple sugars in order to arrive at a full understanding of the contributions to energy excess in populations that are gaining weight.
Energy Balance: Dietary Energy Intake and Population Weight Gain

The evidence that dietary energy intake has increased over decades and that this increase was coincident with the take-off of population weight gain comes from national food consumption data [1, 2, 7]. Such studies show that the increase in food energy supply beginning around the 1970s in the United States provided the appropriate level of exposure to have resulted in the rise in obesity in that country beginning in that decade. Similar conclusions have been drawn about the food energy supply and the timing of the obesity epidemic in the UK. The increase in food energy supply was related to increased consumption of some foods such as cereals as well as an increase in the intake of fats, oils and simple sugars in the form of sweetened drinks. In an economic model, consumption is driven both by availability and price, but in addition also by successful marketing, and all three variables have apparently altered dramatically within the time frame of the epidemic. Industrialization and globalization as they have affected economic and social life in African-origin populations have had identical effects on food and implicitly dietary energy intake [28].

Conclusions

After centuries wherein the challenge has been the maintenance of body-weight in the face of marginal food security, there has been an abrupt uptick in the rate of rise of relative weight globally which began insofar as we can ascertain in the 1970s and the 1980s. This has led to high and increasing rates of overweight and obesity in high-income countries worldwide, but also an alarming inclusion of low- and middle-income populations in this obesity epidemic. The precise drivers of these concurrent epidemics are not agreed, but probably include, on the one hand an increase in dietary energy intake resulting from the impact of industrialization and globalization on food availability and price. On the other, there is the documented steady reduction in activity energy expenditure derived from muscular power as an input into economic production as well as on household and leisure activities. This fall in physical activity energy expenditure has been underway since at least the start of the industrial revolution three centuries ago without an apparent rise in population weight gain. Dietary energy intake is thus highlighted as the probable major determinant of this weight gain. The rise in population weight without accompanying linear growth manifests as obesity. The accretion of fat as well as the response to other environmental exposures during progressive industrialization and modernization is associated with cardiometabolic pathology that has huge impact on health as well as macroeconomics. Given the power and presumed irreversibility of industrialization and globalization, our ability to reverse these obesity epidemics is heavily dependent on new
knowledge being developed which gives insight with prevention and therapeutic implications on the proximal and distal drivers of this progressive positive energy balance.

References


6 Australian Institute of Health and Welfare (AIHW) and National Heart Foundation of Australia: The Relationship between Overweight, Obesity and Cardiovascular Disease. Canberra, AIHW (Cardiovascular Disease Series No 23), 2004.


Dr. Forrester's research is innovative in taking advantage of studies in disparate environmental contexts to gain new insights about the etiology of obesity and related morbidities, with a focus on hypertension. Populations with a historically high prevalence of undernutrition now face the challenge of obesity and related non-communicable diseases (NCDs). Obesity is growing at a faster rate among the poor than among the wealthy in low- and middle-income countries [1], forcing health care systems to address the challenges of a dual burden of over and undernutrition. Rapidly increasing rates of obesity among children and adolescents are also alarming, and may lead to an even greater burden of NCDs in the future.

Dr. Forrester's research demonstrates a clear gradient in the prevalence of obesity and related diseases in African populations living in Africa, the Caribbean, and the United States, although populations in Africa are now experiencing dramatic increases in obesity. Moreover, in these genetically similar populations living in different environments, there are differences in how diseases such as hypertension relate to adiposity, measured by the body mass index (BMI). Dr. Forrester noted that while the cross-sectional BMI-blood pressure relationship appears to be monotonic across populations, the slope of the relationship differs, suggesting physiologic variation that might be rooted in nutritional history. He suggested that in resource-poor settings where undernourishment prevailed in young children, similar gains in BMI may relate to relatively higher increase in blood pressure, and speculated that this may reflect a developmental component resulting in a more reactive cardiovascular system. This is consistent with what was discussed in other sessions: early nutritional insufficiencies may alter susceptibility to subsequent exposures.
Advances in our understanding of the development origins of NCDs in humans is often hindered by the availability of detailed data on child nutritional status and related metabolic changes early in life. Dr. Forrester’s long-term follow-up of Jamaican children who experienced kwashiorkor or marasmus provides very important insights into the long-term consequences of different types of metabolic adaptations in childhood. It is rare to have models in humans that can examine these important physiologic differences in a rigorous way. However, Dr. Forrester noted that it is critical to understand nutritional conditions such as marasmus and kwashiorkor not solely as isolated events which alter the metabolic profile organization of individuals, but rather as a manifestation of phenotypes which reflect susceptibility, that is in turn, influenced by even earlier life events. This is also consistent with other presentations at the workshop that address the meaning of growth, both as a response to a wide range of underlying and proximate factors, as well as a predictor of later health outcomes.

Dr. Forrester’s work suggesting different patterns of metabolic adaptation in children with a history of marasmus or kwashiorkor prompted an interesting set of observations by Dr. Godfrey, which may shed light on brain-sparing mechanisms related to fetal malnourishment. He noted that during fetal life, blood returning from the placenta can go through the liver parenchyma or through the bypass channel of the ductus venosus. Growth-restricted fetuses shunt more blood through the ductus venosus to spare the fetal brain, but some normal fetuses shunt 10% of nutrient-rich blood through the bypass channel while others shunt 60%. From animal studies where the ductus is blocked, this not only changes the blood flow through the liver but it also changes the growth and development of hepatocytes, not just in the short-term but in the long-term. So, he suggested that some of these different metabolic responses may potentially be entrained by exposure of fetal hepatocytes to different nutrients coming from the placenta, perhaps switching the epigenetics of those hepatocytes.

In response, Dr. Forrester noted that one of the fundamental questions that need answers concerns the point in the metabolic pathways that is the primary control being exerted for micronutrient partitioning. Studies in the Pima Indians show that different individuals partition fat to oxidation versus lipogenesis, so understanding whether that’s at the level of the mitochondria or at a different hepatic level is important. Similarly, the nature of the demand and its balance with protein breakdown plus dietary supplies of amino acids to fit the demand of protein targeting are important. The observation that severely stunted children have a greater propensity to accumulate fat intra-abdominally and to display a higher cardiovascular risk also shows that early nutritional/metabolic status has an impact on the likelihood of accumulating energy balance surplus. All of this work suggests there are many levels worthy of further investigation in both animal and human models.

Dr. George raised an additional question about the age at which nutritional conditions such as kwashiorkor typically manifest, noting that classically
kwashiorkor was described in toddlers. Dr. Forrester noted that as the prevalence of severe malnutrition has declined, cases admitted to the hospital show considerable variation in etiology. His experience is that there are secular trends in the type of baby now exposed to cumulative undernutrition and the type of baby that eventually presents at the hospital. Thus, he suggested that the road to produce undernutrition and the underlying susceptibilities has changed in Jamaica, and a similar phenomenon may be occurring in India and other parts of the world.

Turning to what is driving the excessive weight gains observed in so many populations worldwide, Dr. Forrester highlighted the importance of drivers of weight gain, including changes in appetite and dietary energy intake as well as physical activity. His work emphasizes the need for precise, objective measurements of these factors. Discussion focused on the role of diet composition. Dr. Forrester raised the notion of a ‘protein target’. When protein is abundant (true for the typical western diet, comprised of about 16% protein), individuals may consume varying amounts of carbohydrates and fat and still meet protein needs. However, when the kind of food easily available is largely energy rich but nutrient poor, the prediction would be that people will overconsume in an attempt to reach a protein target. This would be the case, especially for children in poor countries where the food security emphasizes energy as opposed to nutrients.

Dr. Forrester extended the notion of the protein target to help understand how the maternal diet and energy balance during pregnancy may play a role in long-term outcomes. He cited the work of Campbell et al. [2], showing a very tight relationship between maternal size (interpreted as a proxy for metabolic competence) and intrinsic physical activity. He speculated that the approach to dietary intake during pregnancy (notably ways to achieve the protein target) might condition a physiological control of appetite as well as physical activity. A key research need is therefore to understand nutrient partitioning and metabolic responses to different patterns of maternal dietary intake during pregnancy and their consequences for infant and activity and responses to diet.

The discussion also touched on the role of other dietary factors in hypertension. Dr. Haschke asked about the role of sodium and potassium, and their ratio, in relation to population differences in hypertension. Dr. Forrester noted his preference to look at the intake of minerals within the context of dietary patterns. An increased sodium:potassium ratio can come from increased salt intake or reduced potassium intake, but the ratio says nothing about the total exposure, which can vary substantially. His view is that mineral intake in ecologic studies describes the overall food environment, capturing the quantity of food and perhaps the industrialization of food rather than just the mineral stimulus to raising blood pressure. Potassium intake could represent the degree to which individuals and populations consume a DASH-type diet with useful intake of a wide range of micronutrients included in vegetables and fruits, which have a beneficial effect on blood pressure.
In the context of clinical relevance of this work, Dr. George asked about the age at which we should start screening for cardiometabolic disorders, and whether it should be universal screening or only a risk-related approach based on nutritional history (e.g., low birthweight or child malnutrition) and current status (overweight and obesity). Dr. Forrester noted that as entire populations (including children) are shifting toward a higher BMI, perhaps the screening approach to identify high risk might not be an appropriate strategy. Instead, he suggested that a more complex multifactorial intervention to change behaviors, including pediatric behaviors, might be a better approach. He concluded that the most important implications are not for treatment but how we can influence the factors that affect the child’s diet and the child’s physical activity.

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**References**


State of the Art of Growth Standards

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Abstract

Growth charts have become widely used, if not universal, tools for the assessment of the growth and health of children. In 2006, the WHO published a set of charts designed to represent standards to which all the world’s children should aspire. They were produced in response to the apparent variability in the patterns of child growth documented worldwide, and with the aim of creating a prescriptive standard based on best feeding advice. Our modern understanding and use of growth references arose out of the application of technology, mathematics and charting to the biology of growth in the 19th century. As means of summarizing normal development, modern growth standards have replaced Renaissance conceptions of human form based on idealized proportions in harmony with the cosmos, and the simple reference to key developmental milestones first noted by the ancients. The WHO growth standards are the culmination of a search for a human ideal based on 20th century biology. However, while they may be the ‘best’ standards based on contemporary feeding advice, they are ‘provisional’ because all developmental processes in biology, including body growth, are plastic and permit a flexibility of life course trajectories in response to epigenetic, nutritional and other environmental conditions.

Introduction

In 2006, the World Health Organization (WHO) published a set of charts which may be regarded as the current ‘state of the art of growth standards’ [1]. They are based upon measurements of samples of healthy breastfed infants born of and nursed by healthy non-smoking mothers, from six countries of the world (Brazil, Ghana, India, Norway, Oman and USA) selected to represent a cross-section of
the genetic and cultural diversity of the global population [2]. WHO argued that they are universally applicable and may be considered as not just descriptive, but also prescriptive; in effect standards of growth to which all the world’s children should aspire [3].

Growth charts are graphical ways of describing the rates of growth of indices of body size (most commonly mass and length, but also the dimensions of specific organs and parts of the body). The measurement of the rates and patterns of body growth has become a valuable index of child growth and development. Such measurements correlate well with specific and general health indices, and are now widely used to identify not only ‘failure to thrive’ and obesity, but also to alert pediatricians and public health professionals to the risk of disease and to help them monitor progress and response to treatment.

‘Recent Advances in Growth Research: Nutritional, Molecular and Endocrine Perspectives’ is the subject of this symposium and the aims of this paper are to take a historical perspective – to trace the origins and development of references and standards for ponderal and linear growth (growth in mass or weight, and length or height) and how they have reached the present ‘state of the art’. In doing so, this review focuses largely on the weighing of babies.

**Early History of Child Rearing and Anthropometry**

The care, growth and rearing of children have been subjects of interest to physicians, philosophers and biologists from antiquity – Hippocrates, Aristotle and Soranus all wrote about child rearing, offering advice about infant care, feeding and diet. They focused on the ‘seven ages of man’, documenting milestones, such as teething, weaning, menarche and menopause. Anthropometry was born not of medicine or science, but of the arts, inspired by Pythagorean geometry and Platonic philosophy. Artists sought the ideal proportions of man, believing that a scale of proportions, such as governed the positions of heavenly bodies and the harmonics of music, was also to be found in the physique of the human body. Physical measurement of length tended to be expressed as ratios rather than in absolute numbers [4].

The writings of the ancients informed Renaissance physicians and authors, who rediscovered, supplemented and reinterpreted their teachings. An apt example of thinking about child rearing in the 16th century is *Paedotrophia*, a didactic poem on pregnancy, childbirth, infant care and feeding, subtitled ‘The Art of Nursing and Rearing Children’ [5]. Synthesizing the contributions of classical writers with the new humanistic thinking, this work represents the ‘state of the art’ of infant care before the ‘scientific revolution’ that started to inform medical practice and natural philosophy. In the 17th century observation, measurement and experiment sought objective explanations of the structure and workings of living things, and the human body came to be regarded
as a machine, leading to demonstrable theories of the circulation of the blood (William Harvey 1579–1657) and the fate and effects of food in the body (Sanctorio Sanctorio 1561–1636), for instance. The application of technology (including the weighing balance, microscope and thermometer), coupled with quantitation and charting, led to a new (non-humoral) physiology, and with cellular and tissue anatomy and pathology, to the beginning of the end of Galenic medicine [6]. The iatromathematical approach to ‘natural philosophy’ with the application of measurements of length, weight, temperature etc., to the investigation of living things proved both helpfully descriptive and usefully predictive. The compilation of sequential data on growth invited mathematical analysis and clinical application.

**Early History of Weighing and Charting**

Infant growth charts have their origin in the weighing of babies, a practice that began sporadically in the 17th and 18th centuries [7]. Undertaken by obstetricians searching for an index of the viability of the fetus, the weight of the newborn became an objective measure useful not just for clinical purposes but also to settle disputes about legitimacy. In the early 19th century, large series of the weights of the newborn were collected and reported, mostly from maternity hospitals in Europe, as obstetricians increasingly applied science to their clinical practice (table 1). Taking into account national differences in weight standards before metrification (adopted officially by Napoleon in 1795), measurements of birthweights show considerable variability within a range either side of the modern mean. Such attempts to define the ‘normal’ weight of the newborn were examples not just of the descriptive ‘anatomo-clinical’ method which began to eclipse humoral medicine, but also of the ‘méthode numérique’, the application of mathematics to medicine to measure and analyze clinical phenomena [8].

Adolphe Quetelet (1796–1874) was a pioneer of the development of statistical methods for the analysis of complex biological and social data. He aimed to define the ‘l’homme moyen’ (‘average man’), based on his belief that the average of all human attributes in a given country serves to define the ‘type’ of the nation analogous to the ‘center of gravity’ in physics [9].

‘In order to succeed, we must study the masses with a view to separating from our observations all that is fortuitous or individual. Everything being equal, the calculation of probabilities shows that we approach nearer to the truth in direct ratio to the number of individuals’ [10].

Observing the ‘law of large numbers’ proposed by Siméon-Denis Poisson, Quetelet was one of the first to attempt to define the ‘normal’ growth of infants, collecting the weights of an unknown number of children in the foundling hospital in Brussels [11]. These measurements, which established that girls and
boys grew at different rates, remained the only source of data on infant growth for several decades.

Physicians, physiologists and obstetricians with an interest in the growth and development of the fetus and child started to include simple growth charts in textbooks of pediatrics in the late 19th century, and with the rise of ‘scientific medicine’ weighing, measuring and the documentation of growth became prominent subjects in their opening chapters [12]. The distinction between longitudinal and cross-sectional methods of collecting and using growth data was appreciated, but the early growth charts were relatively simple, with a single curve (mean) and no measures of variance (fig. 1).

### French Consultations de Nourrissons and Gouttes de Lait

With growing medicalization and scientization of infant and child care and feeding [13], measurements of growth became adopted as useful objective indices to inform diagnosis, treatment and prognosis. Pierre Budin, chief of the ‘special care baby unit’ (Pavillon des Enfants Débiles) of the Maternity Hospital

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**Table 1.** Weights of newborn infants in the 18th, 19th and 20th centuries, taken from Tanner [4] and Cone [7]

<table>
<thead>
<tr>
<th>Date</th>
<th>Author</th>
<th>Place</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1753</td>
<td>Roederer</td>
<td>Göttingen</td>
<td>3.09</td>
<td>2.93</td>
</tr>
<tr>
<td>1786</td>
<td>Clarke</td>
<td>Dublin</td>
<td>3.35</td>
<td>3.09</td>
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<tr>
<td>1804</td>
<td>Friedlander</td>
<td>Paris</td>
<td>2.94</td>
<td>(both)</td>
</tr>
<tr>
<td>1830</td>
<td>Quetelet</td>
<td>Brussels</td>
<td>3.20</td>
<td>2.91</td>
</tr>
<tr>
<td>1840</td>
<td>Quetelet</td>
<td>Brussels</td>
<td>3.00</td>
<td>3.00</td>
</tr>
<tr>
<td>1842</td>
<td>Simpson</td>
<td>Edinburgh</td>
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<td>1849</td>
<td>Scanzoni</td>
<td>Würzburg</td>
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<td>3.43</td>
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<tr>
<td>1853</td>
<td>Veit</td>
<td>Berlin</td>
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<td>3.13</td>
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<tr>
<td>1855</td>
<td>Hartman</td>
<td>Rostock</td>
<td>3.54</td>
<td>3.44</td>
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<tr>
<td>1860</td>
<td>Hecker</td>
<td>Munich</td>
<td>3.34</td>
<td>3.22</td>
</tr>
<tr>
<td>1860</td>
<td>von Siebold</td>
<td>Göttingen</td>
<td></td>
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<tr>
<td>1860</td>
<td>Duncan</td>
<td>Edinburgh</td>
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<tr>
<td>1867</td>
<td>Martin</td>
<td>Berlin</td>
<td>3.25</td>
<td>(both)</td>
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<tr>
<td>1871</td>
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<td>1925</td>
<td>Low</td>
<td>Aberdeen</td>
<td>3.48</td>
<td>3.43</td>
</tr>
</tbody>
</table>
Fig. 1. Growth chart used by Pierre Budin in Paris. The dotted line is the mean body-weight and the histogram is a measure of the volume of feeds taken by infants.
in Paris, pioneered the weighing balance and growth chart as essential clinical tools (along with the thermometer and temperature chart) in the care of infants. Based on his clinical use of growth charts in hospital, he established postnatal maternal and infant welfare clinics to monitor the health of the newborn after discharge from the maternity hospital. These Consultations de Nourrissons and Gouttes de Lait were based on three principles: the support of breastfeeding, the weighing of babies and the provision of clean sterilized milk to infants that were not thriving [14]. The consultations proved very effective and popular, and by 1905 there were more than sixty in and around Paris, and soon they were being adopted and reproduced throughout Europe as well as in Great Britain [15] and North America [16].

‘When babies develop normally they put on weight regularly and of a quantity more or less according to their age – this is a general rule. When the curve of weight gain of an infant is good, one can conclude that it is in an excellent state of health, and is in no danger; if it is unwell, one knows that the weight goes down’ [17].

The growth chart chosen by Budin (based on data collected in 1864) did not distinguish boys from girls, neither did it take into account mode of feeding (fig. 1). Nevertheless, it became enormously useful as an objective measure of the health of the newborn, and a guide to the use of artificial feeds. The provision of clean, modified, sterilized milk (du lait de vache de bonne qualité et sterilisé) proved effective not only in improving infant growth (in babies whose mothers could not or were not nursed by their mothers) but also in reducing infant mortality [18].

One of Budin’s colleagues, Gaston Variot, sought to counter the prevailing opinion that the growth of artificially fed infants was generally inferior to that of the breastfed. He published tables of the weights of around 25–40 boys and girls measured each month [19]. The artificially fed did almost as well as the breastfed, particularly in the second half of the year, but the mixed-fed did the best. ‘ . . . There is only a minimal difference between the weights and lengths of the babies raised on the breast or the bottle, if one applies to the latter modern, improved artificial feeds, as is done in the Gouttes de Lait.’ The numbers of infants he weighed may have been small, and Variot’s goal was to champion the effectiveness of the Gouttes de Lait, but his study showed the range of normality within which babies thrived. These data represent one of the first systematic attempts to provide growth standards for infants which distinguish between the sexes and take into account the way babies were fed.

The practice of weighing babies was seized upon by public health authorities throughout Europe, North America and elsewhere (Israel, New Zealand, Uruguay), as a means of combating infant mortality [16]. The milk requirements of infants were defined [20] and by the mid-20th century growth monitoring had become a central component of international child health initiatives. Promoted as a ‘road to health’, the growth chart offered a simple means of charting the trajectory of normal growth and development and identifying deviations from them [21].
Variability of Growth in 20th Century

By the 1970s, a large number of national growth charts was in use, each based on locally compiled data which became used as references against which to compare the growth of children in welfare clinics, school health services and other clinical and public health settings. Analyses and comparisons of the growth curves of these different growth charts show that the rates and patterns of growth in weight of European and North American infants have changed significantly over the last 100 years (fig. 2). Since the development and first use of growth charts for postnatal health surveillance, there appears to have been an increase in the weight of one-year-olds of about 1 kg. Taking into account the higher past rates of infant morbidity and mortality, and poorer quality of artificial feeds, this change is likely to be an expression of the secular increase in physical stature consequent upon improved hygiene and nutrition [22].

Recognition of the variability of the patterns of growth of children worldwide prompted the WHO to set up a working group on infant growth in the early 1990s tasked with compiling new reference data that would be widely applicable. In reviewing the existing references, the working group noted repeated instances of negative deviations in growth rates of healthy breastfed infants compared to the then current WHO references [3]. These were based on growth data collected from predominantly formula-fed infants in the USA in the 1960s and 1970s [23]. The negative deviations in growth (particularly between the 3rd and 6th months) appeared so marked that they encouraged premature introduction of complementary feeding, suggesting that the lactation of women was insufficient to sustain adequate infant growth; or perhaps vice versa [24]. Moreover, the slower weight growth of breastfed babies, both
now and in the past compared with modern formula-fed babies, has implications for our understanding of the risk factors for obesity and cardiovascular disease [22]. The WHO working groups resolved to create a growth reference that also served as a standard – ‘a single international reference representing the best standard possible of optimal growth for all children <5 years of age’ [2].

**Universal but Provisional Growth Standards**

Body growth (change in mass and length) is a composite and complex process throughout the life course, and the WHO growth standards represent the ‘state of the art’ of what we may regard as optimum growth consistent with and defined by our current understanding of human biology (particularly nutrition, genetics and endocrinology). However, the variability of infant growth in time and space, and the plasticity of developmental processes during the life course (fetal life, infancy, puberty, reproduction), mean that the WHO infant growth standards cannot alone be regarded as an ideal growth trajectory for all babies at all times and places. They are *universal*, clinically, in the sense that they represent the best common standard to apply to all the world’s children in a public health setting, but they are *provisional*, biologically, in the sense that they are expressions of changing and changeable processes (cultural as well as endocrinological and nutritional) that regulate growth. Maternal height and age of menarche have changed significantly over the last century, for instance, and so too are other major measureable biological factors such as birthweight (table 1) and lactational capacity likely to change, quite apart from cultural processes like the choice and timing of weaning foods.

This plasticity of growth serves a vital function in both the ontogeny of the individual and the evolution of the species. It permits opportunities to pursue alternative developmental courses, in response to adverse events (such as intrauterine growth restriction or undernutrition in childhood, which may be followed by catch-up growth in infancy or puberty), but these can be associated with penalties or costs later on [25]. Mismatches between genetically determined biological processes and new environmental conditions may well be a significant cause of adult disease as the prevalence of infections and other preventable and treatable causes of chronic disease diminish [26].

‘Initiatives for the development of a uniform standard for human growth use the assumption that optimum health across the life-course will be achieved through comparable growth in various settings, irrespective of factors such as maternal diet, body composition, or physical activity’ [27].

Changes in bodyweight and length are summations of the growth of tissues and organs each of which is subject to its own developmental program, regulated by proximate and remote influences – genetic and environmental factors which determine physiological functions and pathological responses. Different organs
grow at different rates (brain and gut, for instance), and the allometric relations between them, while describable mathematically, are governed by developmental pathways that are part of the life course strategies of different animal species [28]. Developmental plasticity provides individuals with the flexibility to adjust the trajectory of their development to match their environment [26].

Conclusions

One hundred years ago, growth charts were chiefly used to identify children that were failing to thrive; indeed they were vital tools in the battle to combat infant mortality [29]. The current WHO growth charts continue to serve a vital function in monitoring the development and health of the world’s children, especially in countries where growth faltering is a precursor and accompaniment of morbidity and a significant risk for premature mortality [30]. In using the WHO growth standards to compare the growth of babies during the last hundred years, the variability and plasticity of infant growth rates are revealed.

The WHO working group acknowledged that the WHO standards ‘allow for possible future revision as substantial new biological information on the growth of infants and young children becomes available’ [2]. Given the geographical and temporal differences and changes that have been documented around the world in different societies and in different times past, the WHO infant growth standards must be regarded as ‘provisional’ as are all biological ‘indices’ that are subject to variation consequent upon genetic, epigenetic and environmental factors.

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Healthy Infant Growth: What Are the Trade-Offs in the Developed World?

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Abstract

More rapid infant weight gain is associated with long-term benefits, such as better neurodevelopmental outcomes for some infants, but also with harms, such as an increased risk of later obesity and higher blood pressure. Determining the optimal rate of infant weight gain requires balancing these benefits and risks, the magnitude of which appears to differ for specific populations of infants. Among healthy full-term infants, gain in weight-for-length is associated with obesity and adverse cardiometabolic outcomes, with no substantial benefit to neurodevelopment. Preterm infants derive substantial neurodevelopmental benefit from gain in weight-for-length during the neonatal intensive care unit stay, and possibly from linear growth thereafter; excess weight-for-length gain may predict adverse cardiometabolic outcomes. Among full-term SGA infants, evidence is limited; excess weight-for-length gain in infancy may predict later cardiometabolic risk, but does not appear to modify neurodevelopmental outcomes. Future research should consider not just the magnitude but also the value of the various outcomes in each population. More work is also needed to identify shared determinants of rapid early weight gain, cardiometabolic risk, and neurodevelopment, and to differentiate effects of weight gain that is proportional to linear growth from weight gain that is excessive.

Overview of Trade-Offs

Early infancy is a period of rapid fat accumulation, linear and brain growth, and cognitive, motor, and social development. More rapid infant weight gain has been associated with long-term benefits, such as better neurodevelopmental
outcomes for undernourished and preterm infants, but also with harms such as an increased risk of later obesity and higher blood pressure. Determining the optimal rate of infant weight gain requires balancing these benefits and risks. Additionally, the balance of benefits and risks may differ for specific population of infants, for example infants born full term vs. preterm or appropriate vs. small for gestational age (SGA). Here, we review our current understanding of the risks and benefits associated with rapid infant weight gain in these distinct populations.

**Trade-Offs for Full-Term Infants**

As reviewed in a recent Nestlé Nutrition Institute workshop [1], extensive evidence now exists that rapid infant weight gain is associated with later increased adiposity. In one of several systematic reviews, Ong and Loos [2] identified 21 studies, all of which reported positive associations of infant weight gain with later obesity risk. For each 0.67 standard deviation (SD) excess weight gain from birth to 4–24 months of age in the different studies, obesity risk increased 1.26- to 4.55-fold. Other studies have linked rapid weight gain in infancy with cardiovascular risk factors such as higher blood pressure [3]. In one study, more rapid infant weight gain from birth to 6 months was also linked with a higher metabolic risk score, consisting of waist circumference, systolic and diastolic blood pressure, and fasting glucose, insulin, triglycerides, and high-density lipoprotein cholesterol, assessed at age 17 years (fig. 1) [4]. The association of more rapid weight gain with later blood pressure appears to be strongest for infants who were thinnest at birth [5], whereas the association with obesity may not be modified by birth size [6].

With strong epidemiologic evidence that obesity and cardiometabolic risk in general has roots in early rapid weight gain, it is reasonable to consider intervening in some way to moderate early weight gain to prevent later cardiometabolic disease. However, given the rapid brain growth and steep developmental trajectory of early infancy, potential neurodevelopmental harms of such a strategy must be considered.

A body of research focused on ‘weight faltering’ or failure to thrive (FTT), has provided some evidence that particularly slow weight gain early in infancy may lead to poorer cognitive outcomes. However, most studies are limited by poor generalizability and failure to account for size at birth, gestational age, and other confounding variables [7]. One study [8] that examined a regional cohort and defined FTT based on weight gain found that, after adjustment for maternal IQ and organic vs. non-organic etiology of the FTT, the IQ at age 8 years of children with FTT was only 1.7 points lower (95% confidence interval, CI: –5.2, 1.9) than children without FTT. Reading scores were 1.5 points higher (95% CI: –2.1, 5.3) in the children with FTT.
Literature on FTT can provide clues to outcomes among children with extreme weight faltering, but given the strong link between more rapid infant weight gain and later obesity, examining the entire spectrum of infant weight gain with respect to later cognition is more relevant than examining FTT alone. A recent systematic review [9] identified 5 relevant studies of contemporary, full-term cohorts in developed countries. The studies included appropriate for gestational age (AGA) children. Two UK studies [7, 10] found small (<1/10 SD in outcome per 1 SD in weight gain) but statistically significant associations of early weight gain with school age IQ and educational test scores. In one of those studies [10], only early (birth to 8 weeks) but not later (8 weeks to 9 months) weight gain was associated with later scores, and the effect size was small (0.8 IQ points per SD change in weight). Similarly, a Finnish study [11] of full-term infants found that more rapid BMI gain from birth to 5 months was associated with small improvements in general reasoning (1 point per SD BMI gain, 95% CI: 0.2, 1.8) and visual motor integration (2.2 points per SD BMI gain, 95% CI: 1.3, 3.1) at 4 years, but there was no association of BMI or weight gain from birth to 5 months with verbal competence or language comprehension, nor was there an appreciable association of linear growth from birth to 5 months with any of the cognitive outcomes. Those authors also noted a small association of linear growth – but not BMI gain – from 5 to 20 months with visual motor integration. They identified an inverted U-shaped relationship in which both smaller and larger BMI at 20 months were associated with lower visual motor integration scores.

Other studies have found no association of early weight gain with later cognition. For example, in a US cohort [12], we found that neither weight gain from
birth to 8 weeks nor from 8 weeks to 6 months was related to cognition at age 3 years (fig. 2) or at 7 years [Belfort et al., unpubl. data]; findings were similar in a UK cohort [9]. In a Dutch study that compared postnatal weight gain and IQ adolescence in twins, the twin with greater weight gain from birth to 2 years had an IQ 3.2 points lower (p = 0.002) than the twin with less weight gain, although the authors did not account for confounding by birthweight or gestational age, and only 60% of the cohort was born full term. Thus, in healthy populations in developed countries, there is only inconsistent evidence for a small effect of early weight gain on later cognition.

In sum, among healthy full-term infants, ample data support a strong association of rapid infant weight gain with later obesity as well as limited evidence regarding other cardiometabolic disease risk factors. In contrast, studies of early weight gain and later neurodevelopmental outcomes have generally shown small or no associations.

**Trade-Offs for Preterm Infants**

Preterm infants, particularly those born very low birthweight (<1,500 g), often experience poor weight gain and linear growth after birth. Of almost 24,000 preterm infants discharged from a large network of US neonatal intensive care units (NICUs), approximately one third were at less than the 10th percentile for weight and length for age at the time of discharge; the proportion was higher for less mature infants [13]. By school age, most preterm children have attained a weight and height similar to their full-term peers, although males born SGA may remain lighter and shorter into early adulthood [14].

Children born preterm also experience substantial motor, cognitive, and behavioral deficits. On average, at school age, performance on motor testing is

![Graph](image.png)

**Fig. 2.** Estimated Peabody Picture Vocabulary Test (PPVT) score at age 3 and standard error within deciles of infant weight z score at 8 weeks and 6 months. Estimates are adjusted for birthweight z score and other maternal and infant factors. No association between infant weight gain and later PPVT score is seen. Data from 872 participants in Project Viva. From Belfort et al. [12].
nearly 1 SD lower for preterm compared with full-term children [15], and IQ is 11 points lower [16], with differences more pronounced for children born at lower gestational ages.

An important determinant of neurodevelopmental outcome for preterm infants is weight gain during the NICU hospitalization. In a multicenter US study of 495 infants born at <1,000 g and assessed at 18–22 months of age, being in the highest versus lowest quartile of weight gain to from birth to ‘status’ (discharge, transfer, 120 days of age, or 2 kg) was associated with higher Bayley cognitive (2.3 points, 95% CI: 1.0, 4.9) and motor (1.9 points, 95% CI: 0.9, 4.3) scores, an 8-fold reduction in cerebral palsy, and a 2.5-fold reduction in neurodevelopmental impairment [17]. That study did not examine the role of BMI gain or linear growth. In an Australian cohort of preterm infants <33 weeks’ gestation that also measured Bayley scores at 18 months, we found that BMI gain through term (40 weeks’ postmenstrual age) was associated with better motor (2.5 points per z score weight gain, 95% CI: 1.2, 3.9) and cognitive (1.7 points, 95% CI: 0.4, 3.1) scores at 18 months (table 1) [18].

Combined results from parallel randomized trials of a protein-, calorie-, and mineral-enriched preterm formula either as the sole diet (trial A) or as a supplement to mother’s milk (trial B) also support the importance of NICU growth for optimizing brain development. As compared with children who received a standard term formula, children who received the preterm formula had faster NICU weight gain (15.8 vs. 13.3 g/kg per day, p < 0.001) and better neurodevelopmental outcomes at 18 months (2.6 Bayley cognitive points, 95% CI: –1.7, 6.9; 6.2 Bayley motor points, 95% CI: 2.4, 10.0, and 4.5 social quotient points, 95% CI: 1.3, 7.7) [19]. Follow-up of the cohort to school age revealed a persistent cognitive benefit of the preterm formula, with a stronger effect in boys (6.5 IQ points, 95% CI: 0.5, 12.5) versus girls (1.3 points, 95% CI: –4.3, 6.9) [20], and in a subset of original trial participants followed to adolescence, larger caudate and hippocampus volumes on MRI [21]. Based on this evidence, use of preterm formulas and nutrient enrichment of human milk are routine practices in contemporary NICUs.

While the importance of NICU growth for later neurodevelopment is well documented, relatively few studies have examined the importance of infant growth after NICU discharge, and even fewer have separated effects of growth after discharge from growth during the NICU hospitalization. In our analysis of a multicenter US cohort of preterm (<37 weeks), low birthweight (<2,500 g) infants born in the 1980s, greater weight gain (2.1 points per SD, 95% CI: 1.1, 3.1) and linear growth (2.4 points per SD, 95% CI: 1.3, 3.5) from term to 4 months corrected age – but not from 4 to 12 months of age – were associated with higher IQ scores at age 8 years [22]. Similarly, in a contemporary Australian cohort born between 2001 and 2005, we found that greater weight gain and linear growth from term to 4 months were associated with better motor scores at 18 months (table 1) [18]. In neither of those studies was infant gain in
weight-for-length from term to 4 months associated with later neurodevelopmental outcome, suggesting that in the earliest months after NICU discharge – which typically occurs around term – linear growth is beneficial, but weight gain out of proportion to linear growth is not. These post-discharge observations contrast with findings during the NICU hospitalization, during which excess weight gain does appear to benefit later neurodevelopment. Later infancy (4–12 months) gain in weight-for-length was associated with better outcomes in one of those studies [22] but not the other [18].

Observational studies support modest benefits of more rapid post-discharge linear growth, but results from a UK randomized trial [23] do not. At 9 months of age, preterm infants who had been randomized at discharge to receive a post-discharge formula enriched with protein, calories, and minerals were 0.36 kg heavier (95% CI: 0.04, 0.69) and 1.1 cm longer (95% CI: 0.31, 1.89) compared with infants who received a standard term formula, but at 18 months there were no measureable differences in weight or length, or in cognitive or motor function. That trial did not report results of growth in terms of weight-for-length, but a different UK study [24] reported that feeding a similar post-discharge formula led to increased lean mass and decreased fat mass percent measured by dual energy X-ray absorptiometry in male preterm infants, with no differences observed among females.

While interest in neurodevelopmental outcomes in preterm infants is longstanding, more recently, researchers have begun to focus on their cardiometabolic health, and emerging evidence suggests that preterm infants may be at

| Table 1. Adjusted associations of infant growth with 18-month Bayley scores |
|---------------------------------|----------------|----------------|
|                                  | Week 1 to term | Term to 4 months |
|                                  | (n = 561)      | (n = 550)       |
| **MDI**                          |                |                |
| Weight gain                      | 2.4 (0.8, 3.9) | −0.4 (−1.9, 1.1) | 0.3 (−1.7, 2.3) |
| Linear growth                    | 0.3 (−1.0, 1.7) | 0.4 (−1.2, 1.9) | −0.9 (−2.5, 0.6) |
| BMI gain                         | 1.7 (0.4, 3.1) | −0.1 (−1.5, 1.3) | 0.8 (−0.8, 2.4) |
| Head growth                      | 1.4 (−0.0, 2.8) | −0.5 (−2.2, 1.1) | −0.0 (−1.7, 1.6) |
| **PDI**                          |                |                |
| Weight gain                      | 2.7 (1.2, 4.2) | 1.7 (0.2, 3.1) | 0.1 (−1.9, 2.0) |
| Linear growth                    | 0.8 (−0.5, 2.1) | 2.0 (0.7, 2.3) | 0.3 (−1.1, 1.6) |
| BMI gain                         | 2.5 (1.2, 3.9) | 1.2 (−0.2, 2.5) | 0.9 (−0.8, 2.6) |
| Head growth                      | 2.5 (1.2, 3.9) | 0.2 (−1.3, 1.8) | 0.6 (−0.9, 2.1) |

Figures represent linear regression estimate of points per z score increment (95% CI). MDI = Mental development index; PDI = psychomotor development index. Term is 40 weeks' post-menstrual age. Other ages are corrected for prematurity. Estimates adjusted for child and parental factors. From Belfort et al., in press.
increased risk for cardiovascular disease in adulthood. In adolescence and young adulthood, our meta-analysis of observational studies shows that former preterm infants have approximately 2.5 mm Hg higher systolic blood pressure than full-term infants (fig. 3) [25], and are about twice as likely to be hypertensive as adults [26]. Finnish, Dutch, and New Zealand groups have reported greater insulin resistance in preterm compared with full-term adolescents and young adults [27–29], and preterm infants appear to be at about 60% higher risk to develop type II diabetes later in adulthood [30]. Fat mass in childhood appears to be lower and lean mass higher in preterm versus full-term infants, but truncal fat relative to arm fat deposition is greater [31].

While promoting more rapid infant weight gain, at least during the NICU hospitalization, is clearly beneficial to neurodevelopment, it is also possible that promoting more rapid weight gain could harm cardiometabolic health. Some experimental evidence supports this concern. For example, a subset of preterm children randomized in 2 parallel trials to receive a protein-, calorie-, and mineral-enriched preterm formula from birth through hospital discharge had higher fasting levels of 32–33 split proinsulin in adolescence, which may indicate greater insulin resistance, as compared with children who received banked donor breast milk or standard formula [32]. Additionally, children who received the preterm formula had higher diastolic (but not systolic) blood pressure versus children who received banked donor breast milk (3.2 mm Hg, 95% CI: 0.6,
5.8) but not versus children who received the standard formula [33]. In terms of body fat, in a different UK trial of a post-discharge protein, calorie, and mineral enriched vs. standard formula, boys (but not girls) who received the enriched formula for 6 months demonstrated faster weight gain and had greater lean mass as measured by DXA at 12 months, compared with boys who received the standard formula.

Observational studies have provided inconsistent evidence that early rapid weight gain is associated with later cardiometabolic risk in preterm infants. In terms of blood pressure, in 2 studies [34, 35] that included infants born <32 weeks, there was no association of infant weight or weight gain with blood pressure at school age or in late adolescence. We found a small (~1 mm Hg per SD weight gain) association of weight gain and linear growth from term to 4 months with systolic blood pressure at 6.5 years, and of gain in weight-for-length from 4 to 12 months with later systolic blood pressure [22]; the associations of weight gain and linear growth with later BP were seen only in the more mature (>32 weeks’ gestation) infants. A study [27] of preterm infants <28 weeks’ gestation found that those in the highest quartile of systolic BP at age 21 years had been heavier and longer in infancy than those in the lowest BP quartile, suggesting that more rapid weight gain was associated with higher blood pressure, although this finding may be confounded by birth size and/or gestational age.

In terms of insulin resistance, a Dutch study of 345 infants <32 weeks and/or <1,500 g reported a weak association of weight gain through 3 months of age with the log insulin concentration on fasting blood specimen at age 19 years, but no association with c-peptide or log HOMA-IR levels [36]. Further study of a subset (n = 37) of the same cohort at age 21 years revealed that children in the lowest quartile of insulin sensitivity – measured by the euglycemic-hyperinsulinemic clamp method – had been longer at 12 months and heavier at 24 months, but not earlier in infancy, compared with children in the highest quartile of insulin sensitivity, although these results reflect birth weight as well as weight gained after birth. More rapid infant weight gain in preterm infants has also been linked with obesity at age 8 years (odds ratio 2.7, 95% CI: 1.9, 3.9) per 100 g additional weight gain in the first year) [37], and with higher BMI (0.2 SD per SD additional weight gain from birth to 3 months) and greater body fat and abdominal fat percentage as measured by DXA at age 19 years [38].

Thus, among preterm infants – particularly very low birthweight infants most vulnerable to neurodevelopmental impairments – the rationale is strong during the NICU hospitalization to promote rapid weight gain, even out of proportion to linear growth, in the interest of optimizing neurodevelopmental outcomes. In contrast, limited evidence suggests that after term, excess weight gain out of proportion to linear growth does not have substantial neurodevelopmental advantages, and may contribute to cardiometabolic risk later in life.
Trade-Offs for SGA Infants

In contrast to preterm infants who show slow early postnatal weight gain, full-term SGA infants tend to experience rapid gains in length (and weight) in the first months after birth, typically catching up to their AGA peers by 6–12 months of age [39]. Similar to preterm infants, infants born at term but SGA appear to have poorer neurodevelopmental outcomes than those born AGA [40, 41], although effect sizes are much smaller. While numerous studies have identified associations of lower birthweight with later cardiovascular disease risk factors, relatively few have specifically examined populations of full-term SGA infants. In the few studies that have, full-term SGA infants appear to be more prone than AGA infants to hypertension [42] and insulin resistance [43] in childhood, suggesting an increased risk for cardiovascular disease risk later in life.

In terms of the link between infant weight gain and later cardiometabolic disease among full-term SGA babies, in the Collaborative Perinatal Project cohort in the US, increasing weight z score by at least 1 from birth to 4 months and 4 months to 1 year predicted a higher incidence of high blood pressure at age 7 years [44]. Another [45] study found a linear association of faster weight gain from birth to 16 weeks with higher BMI at school age. More rapid early infant weight gain has also been linked to insulin resistance in adolescence [46].

Two randomized trials in the UK aimed to promote more rapid infant weight gain by feeding full-term SGA infants a protein-, calorie-, and mineral-enriched formula; the trials differed by inclusion criteria (study 1, birthweight <10th vs. study 2, <20th percentile) and length of the intervention (study 1, 9 months vs. study 2, 6 months). Combined follow-up of a subset of participants revealed that by school age, as compared with children who received the standard formula, children who received the enriched formula had similar BMI but greater fat mass index as measured by bioelectrical impedance (measured in study 1 participants only; 36%, 95% CI: 10, 68), although not as measured by deuterium dilution (measured in study 2 participants only; 0.6%, 0.1, 1.4) [47]. Children in study 1 who received the enriched formula also had higher diastolic blood pressure (3.5 mm Hg, 95% CI: 0.7, 6.2), and systolic blood pressure was also higher, but not statistically significant (2.0 mm Hg, −1.3, 5.3) [48].

Given the potential cardiometabolic harms of more rapid early postnatal weight gain, it is also important to examine the potential benefits of rapid weight gain to later neurodevelopment. Most studies of SGA infants have focused on preterm children, or combined full-term and preterm children, despite the fact that benefits of early growth to later neurodevelopment may differ for full-term and preterm infants. We could identify only one observational study of neurodevelopment in full-term SGA infants that isolated effects of early infant weight gain from weight gain later in childhood, and also accounted for size at birth. In an analysis of data, the Collaborative Perinatal Project, both slower and more rapid weight gain from birth to 16 weeks (inverted J-shaped relationship) were
associated with lower IQ score at age 7 years (fig. 4) [45]. A randomized trial in the UK demonstrated that feeding full-term, SGA infants a protein-, calorie-, and mineral-enriched formula for 9 months led to improved linear growth that was sustained to 18 months [49], as compared with feeding infants a standard term formula. However, neurodevelopmental outcomes at age 9 months were slightly poorer among infants who had received the enriched formula, and no different at 18 months [50].

In summary, full-term SGA infants appear to be at increased risk relative to AGA infants both for neurodevelopmental deficits and for cardiometabolic disease later in life. Limited evidence suggests that more rapid weight gain may increase the risk for insulin resistance, high blood pressure, and increased fat mass, but not improve neurodevelopmental outcomes.

**Conclusions and Recommendations for Future Research**

Defining the optimal rate of infant weight gain requires balancing its risks, primarily later obesity and related cardiometabolic consequences, with its potential benefits, chiefly healthy brain growth and neurodevelopment. Current evidence suggests that the magnitude of benefit versus harm differs for healthy full-term, preterm, and SGA populations. Among full-term infants, gain in weight-for-length is associated with obesity and adverse cardiometabolic outcomes, with no substantial benefit on neurodevelopment. Preterm infants derive neurodevelopmental benefit from gain in weight-for-length during the NICU stay, and
possibly from linear growth thereafter. Although based on less evidence, excess weight-for-length gain may predict adverse cardiometabolic outcomes. Among full-term SGA infants, evidence is even more limited; excess weight-for-length gain in infancy may predict later cardiometabolic risk, but does not appear to modify neurodevelopmental outcomes (table 2).

Future research should consider not just the magnitude but also the value of the various outcomes of more rapid weight gain. For example, for preterm infants, children and their families may value improved neurodevelopmental outcomes more highly than preventing high blood pressure, thus favoring more rapid early weight gain despite cardiometabolic harms. Educational and health care costs incurred by society in caring for children with these sequelae should also be considered. Decision analysis provides a quantitative framework by which to incorporate data from many sources to analyze these risks and benefits, and will be useful in defining ‘healthy’ growth for various populations of infants.

Prior to considering interventions to moderate infant weight gain, one must first identify its determinants, with a particular focus on shared determinants of early weight gain and later neurodevelopment and cardiometabolic outcomes. Some are likely to be modifiable, for example infant diet and parental feeding practices. Others, such as genetic and hormonal influences, will be less so. The ability to alter patterns of early weight gain and linear growth may be greater for preterm infants, whose intake is strictly controlled during the NICU hospitalization, than for healthy full-term infants. Weight gain accounts both for linear growth and for weight attributable to adiposity. Future work should attempt to differentiate effects of weight gain that is proportional to linear growth from weight gain that is excessive. Timing of growth also impacts potential

Table 2. Summary of neurodevelopmental benefits and cardiometabolic risks of more rapid infant growth in developed countries

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<th>Healthy full-term AGA</th>
<th>Preterm</th>
<th>Full-term SGA</th>
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<td></td>
<td>linear growth</td>
<td>gain in weight-for-length</td>
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<td>Neurodevelopment</td>
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<td>metabolic risk</td>
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↔ ↔ = No association; + = positive association; ? = insufficient evidence.
¹ Gain in weight-for-length during NICU hospitalization associated with better neurodevelopment; weight-for-length gain after NICU discharge appears less important.
interventions; future studies of infant weight gain should attempt to identify narrow windows of time that are most sensitive to later neurodevelopmental and cardiometabolic effects.

References


Healthy Infant Growth: What Are the Trade-Offs in the Developed World?


Discussion on Growth Standards and Trade-Offs in Healthy Infant Growth

Introduction

The third session was titled ‘What is healthy growth?’ The framing of this question implies that the answer can be known. However, in earlier sessions it had been noted that what is healthy for one person or one situation, might not be healthy for another. These conditionalities were explored throughout the third session.

The first talk (by Dr. Weaver) focused on the description of growth and the second (by Dr. Gillman) started to try to interpret growth, with particular reference to the growth of preterm and small for gestational age infants in developed countries. The discussion is summarized under headings related to description and interpretation, although there was interchange and synergy between them. Considerations for future research are combined.

Describing Infant Growth

Dr. Weaver described the history of the development of growth charts, most recently culminating in a set of universal standards for early childhood growth issued by the World Health Organization (WHO) [1]. The description of growth was originally the province of the arts, and its capture by science and then clinicians followed a series of apparently logical steps. These steps started from trying to describe normal or average growth and to what extent it varied between individuals. By putting limits on the variation that could be tolerated, it was hoped to understand when growth was abnormal, assess what was associated with abnormal growth (for example diarrheal illness) and then to use growth as an indication for diagnosis or therapy.

A difficulty with this approach is that, by focusing on the abnormal, it implies normal (defined statistically) growth is healthy without substantiating
this position. This has two dangers. First, individuals can have unhealthy patterns of growth whilst still maintaining growth parameters within the normal range. Second, where high proportions of children in a population have unhealthy growth, reference charts based on such populations can ‘institutionalize’ such patterns of growth. Indeed it was noted that this had occurred in countries which had constructed growth charts using measurements from populations of children where many were at risk of becoming overweight or obese [2]. The WHO charts had been designed to overcome the latter problem, and represented aspirational rather than simply descriptive growth standards.

A ‘straw poll’ at the start of the session had shown that many workshop participants were using growth charts for multiple reasons – public health monitoring and decision-making, clinical care, routine child health surveillance, and as a tool for research. Expecting one set of growth standards to fulfill all these functions was challenging. Many workshop participants commented that the aspirational nature of the standards made them difficult to use on a day-to-day basis. The WHO standards were based on advantaged children and families. However, plasticity of growth has likely developed to allow each individual to optimize their physical development to their environment. In resource poor settings, where disadvantage was a common experience, it was possible that children appearing to falter on growth charts were enacting survival mechanisms that were redundant for their more advantaged peers. However, it was also noted that food insecurity can coexist with childhood obesity in the same communities, and even in the same families.

The predominant concern with using the WHO charts was amongst pediatricians from resource-poor settings. In discussion, they questioned the genetic applicability of the standards to the populations that they served. It was noted that growth curves represent average growth and do not take into account the fluctuations that characterize individual children’s height and weight gain, particularly over short periods.

Dr. Weaver stressed in discussion that the new growth standards were the best we have so far but that they are, of necessity, provisional. They are provisional because they depend on current knowledge, which is incomplete, and because they represent changing and changeable processes. Furthermore, as will be discussed later, these changing processes themselves vary by person, time and place. As Dr. Weaver put it, ‘as developmental biologists, we know that nothing is fixed, no biological measure really has an unchanging value’.

**Interpreting Infant Growth**

Dr. Gillman presented the first of a number of talks that tried to interpret infant growth, including deciding whether it was ‘healthy’ or not. The discussion repeatedly acknowledged that growth was nearly always an indicator of
presumed health or pathology rather than an end in itself. Furthermore, growth was represented by proxies or summary measures. There was a tendency to use static measures of size at a point in time rather than dynamic measures such as gain. Many of the studies cited in the literature referred to infant weight or weight gain. However, it was almost certain that this was due to the dominance of weight in medical and other records. There was no a priori reason to favor weight (or weight gain) as the preferred summary indicator, even in relation to excess accumulation of body fat. In relation to cognition, for example, head size might in theory be a better indicator [3].

Dr. Gillman's talk contrasted three groups of infants in a developed country setting – those with a birthweight and gestation in the normal range, those with intrauterine growth restriction (small for gestational age), and those born prematurely. In a comprehensive review of the literature, he considered how the relationships of infant growth in each group were related to later health and other outcomes. However, many common diseases and measures of (adult) human capital have no or few intermediate biomarkers. This meant that there were many more studies describing the relation of infant growth to cognitive or physiologic function (for example, intelligence quotient or blood pressure) and to cardiovascular risk factors, than to diseases, such as some cancers, with high burden but no biomarkers in early to mid-life [4]. When long-term follow-up had been achieved, it was tempting to dismiss the infant experience of babies born decades ago as irrelevant to modern neonatal practice and children's lives.

Much discussion focused on whether observed relationships indicated causation. With few trials, particularly for normal-weight term infants, this was difficult to determine. The PROBIT trial [5] had studied the outcome of prolonged breastfeeding at a population level, and there had been informative trials of supplemental feeding in preterm or growth-restricted infants [6]. However, most of the evidence came from observational epidemiological studies, and this was unlikely to change. Furthermore, infant feeding and growth might well demonstrate complex relationships including reverse causality, with patterns of growth triggering changes in infant feeding.

The discussion recognized that doubt about causality colored actions both at clinical and public health levels. Furthermore, even the relationships that were relatively well described – for example the better neurodevelopmental outcomes in preterm infants with early rapid gain in weight for length – were not well understood in terms of the mechanisms underpinning those relationships. Without some understanding of these mechanisms, it was difficult to know whether changing infant growth by any means would be associated with a change in the outcome in the predicted direction. This hampered the development of interventions.

The focus of Dr. Gillman's talk was the concept of ‘trade-off’ in infant growth and its varying nature in relation to possible consequences of different patterns
of early growth. Trade-off might vary according to the nature of the outcome, for example neurodevelopmental gains in childhood might be more highly valued than decreased cardiovascular risk in adult life. Such outcomes might also be valued differently by the parents of, for example, preterm children, by the children themselves as they aged, and by those who fund health or educational services. They might also be valued differently now and in the future, although economic discounting allowed some quantification of this.

As well as a societal view of trade-offs, the evolutionary view was discussed. In the evolution of human physiology, the rate of infant weight gain was likely to have been positively associated with infant survival from infectious disease, historically a major cause of death. Immediate survival would have been placed above possible increased risks of chronic disease in mid- to late adult life. The decline of infant infectious diseases is recent, so human physiology may still be tipped to favor rapid infant weight gain for evolutionary reasons. The obesogenic environment and an increasingly prevalent view that rapid weight gain is normal [7] then combines to promote a pattern of growth that is no longer advantageous.

Finally, there was discussion of the size of the relationship between infant size and growth, and subsequent outcomes such as blood pressure. Much of the literature describes relative risks. The absolute differences in outcomes, such as blood pressure, between groups of infants with different growth experience were often small. However, even small differences, though clinically irrelevant for individuals, might be important for the health of populations [8].

Recommendations for Research

Describing Growth

Over the centuries, measurement of infant growth has moved from art to mathematical variation. Further development of the description of infant growth needs to

- Develop and implement methods to describe and distinguish informative growth trajectories. Growth is not linear in infancy, yet we mostly study patterns of gain as if it were. Informative growth trajectories may need to take account of ethnic and genetic characteristics.
- Include measurements other than weight, particularly those which allow some assessment of possible causal mechanisms.
- Consider the relationships between pre- and postnatal growth, using longitudinal data.
- Describe the context in which growth is taking place, so that its relevance to other times and settings can be assessed. This applies particularly to translating research evidence between settings with different nutritional milieu.
Interpreting Infant Growth

Many studies in developed country settings have related infant growth to later health outcomes, yet we find it difficult to use this evidence to benefit today’s babies. Further research needs to

- Develop the classification of phenotypes. It is likely that many babies who are within the so-called ‘normal range’ for size and growth exhibit growth patterns that are unhealthy for them as individuals.
- Make values explicit when discussing trade-offs, including specifying what is being valued, by whom and when. Decision analysis is one possible technique to consider. Ensure that the views of parents and the public are included in setting research agendas and interpreting research findings.
- Examine underlying mechanisms with a view to:
  - assessing causation and timing of causation
  - identifying modifiable risk
  - for modifiable risk, quantifying attributable risk and population attributable risk to assess the potential for health gain
  - testing (potentially through randomised trials) possible interventions
  - reducing inequities (disparities) in unhealthy growth.

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What Is Healthy Growth?

Gillman MW, Gluckman PD, Rosenfeld RG (eds): Recent Advances in Growth Research: Nutritional, Molecular and Endocrine Perspectives.

Relationship between Childhood Growth and Later Outcomes

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Abstract
Many studies in different settings and times provided us with enough evidence of the association between environmental exposures (mainly nutrition) during pregnancy/infancy and later health outcomes, such as adult non-communicable diseases (NCDs). An individual with a given susceptibility will continue to experience new environmental challenges (e.g. growth), and these later experiences will modulate the early ones. Children that are thin in infancy and then become larger are at greater risk for later NCD. Studies demonstrated that rapid weight gain is a strong predictor of later NCD, independently of the birthweight. But which periods imply a greater risk for developing NCD? Two periods in the first years of life have been linked to the early obesity onset: the first 6 months and between 2 and 5 years of age. And when do these later health outcomes appear? The literature suggests that they start long before adulthood. Children with rapid weight gain have greater risk for hypertension and cardiovascular disease in the first years of life. These lines of evidence suggest that future research should be committed with educational programs and preventive actions focusing on better life behavior in childhood, adolescence and pregnancy.

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Many observational epidemiological studies in different settings and times, as well as many intervention studies in animals and some in humans provided us with enough evidence of the association between environmental exposures (mainly nutrition) during pregnancy/infancy and later health outcomes, such as adult non-communicable diseases (NCDs). The existence of critical developmental windows has been postulated to explain these long-lasting effects on organs or tissues. During these critical periods, body structure and/or function
would adapt themselves to cope with non-adequate conditions, and this adaptation could have high costs depending on the future life circumstances [1].

An individual with a given susceptibility, in fact, will continue to experience new environmental challenges, and these later experiences – such as nutritional status, infections and social conditions – will modulate the early ones. For instance, thinness at birth has been found to be related to cardiovascular disease (CVD) in adulthood, but mostly among those who were poorer in childhood [1]. Likewise, there is substantial evidence telling us that the incidence of NCD in adulthood depends greatly on the growth experience during childhood [1, 2]. This means that the growth pattern interacts with the individual susceptibility increasing or diminishing the risk of disease. This last subject is the one on which we want to focus our attention.

It has been known for some decades that the risk of CVD is related to adult height in different populations [3]. Adult height is a good proxy of child growth. Although confounding factors could explain part of this association, it seems that the effect remains after adjustments. Because of potential recall bias and lack of information, these associations are better studied in longitudinal studies. These are expensive and need a long time to start producing results. Nevertheless, the literature offers us a good amount of them, like the Finnish Helsinki Birth Cohort Study (individuals born in 1924–1933 and in 1934–1944) [1], the Brazilian birth cohorts of Ribeirao Preto (born in 1982) [4] and Pelotas (born in 1982–1993–2004) [5], the INTV study in Guatemala (younger than 7 years in 1969 and born in 1969–1977) [6], in Philippines the Cebu cohort (born in 1983–1984) [7], in India the New Delhi cohort (born in 1969–1972) [2] and in South Africa the Soweto cohort (born in 1990) [8]. The adult outcomes that have been studied are CVD, hypertension, diabetes, and obesity among others.

Changes in weight patterns are normally analyzed in these studies. For instance, in a follow-up study with 1,094 subjects from Ribeirao Preto, we have found that diastolic adult pre-hypertension and hypertension were independently associated with lower ponderal index at birth and higher body mass index (BMI) at school age [unpubl. data]. On the other hand, the Consortium of Health-Orientated Research in Transitioning Societies found that weight gain at any age during childhood is associated with elevated adult blood pressure [9]. Similar findings were replicated in different settings and with different outcomes. It seems that children that are thin in infancy and then become larger are at greater risk for later NCD. Coronary heart disease (CHD) risk, for instance, was associated with smaller babies at birth followed by an above-average BMI during later childhood [1] (table 1). The highest probability of having CHD is among those that were larger at 12 years but thinner at 2 years (hazard ratio = 3.0).

The same patterns have been described for children that later developed diabetes mellitus (DM). In the New Delhi cohort, the highest prevalence of
impaired glucose tolerance and diabetes was among subjects who were in the lowest third of the group with respect to body mass index at the age of 2 years and the highest at the age of 12 years [2]. It is important to underline that not necessarily the larger size at childhood means obesity. The rapid weight gain is more important than the anthropometric diagnosis itself.

Another important aspect to be considered is the age at which the adiposity rebound (AR) occurs. AR is the lowest point on the BMI curve. In normal children with future normal BMI, it occurs around 6 years of age [10]. Early AR can be associated with excessive adipocyte multiplication [11] that is linked to later obesity. It has been seen that AR occurring before 5 years is highly associated with future type 2 DM (fig. 1). The commutative incidence of type 2 DM was more than 4 times higher among those Finnish children that had AR before 4 years of age when compared with those who had it after 8 years [1].

The individual growth pattern is essential to assess risk for adult NCD. In the New Delhi study, it was seen that future adults with impaired glucose tolerance and diabetes had a BMI drop between birth and 2 years of age, and after that they had an accelerated increase in BMI. Again, only 3.3% of them were overweight at the age of 12 years, and none were obese [2].

Weight gain is associated with other adult outcomes: osteoporosis, final schooling, and some biomarkers as well. For instance, C-reactive protein (CRP) is a mediator of atherosclerosis and chronically elevated levels predict cardiovascular outcomes. It has been found that males who were stunted at 2 years and centrally obese at 23 years had the highest CRP levels [12].
In summary, a rapid weight gain is a strong predictor of later NCD, independently of the birthweight [13]. But which periods imply a greater risk for developing NCD?

Two periods in the first years of life have been linked to the early obesity onset: the first 6 months [14] and between 2 and 5 years of age [15, 16].

Different countries found similar results. The US Project Viva, a cohort study that followed up 1,401 children, found out that a rapid increase in weight for length in the first months of life was an important risk for obesity at 3 years of age [14]. The French Fleurbaix-Laventie Ville Santé study (FLVS II) that followed the growth of 468 children up to the age of 12 years observed two critical periods for the development of adolescence obesity: the first semester and from 2 years onwards [16]. The English Avon Longitudinal Study of Parents and Children has collected data from birth up to 15 years of age of 625 children, and found the age range of 7–9 years as the one with greatest weight gains [17] – in contrast to previous UK studies [18]. In Brazil, the Pelotas cohort failed to show any evidence of a specific period with a greater contribution, but demonstrated that the fat mass:lean mass ratio was strongly associated with weight gain from 4 years onwards [19]. And finally, in a study we conducted among slum children in the city of Sao Paulo, we found that obesity at age 10 was linked with rapid weight gain in the first semester of life and at 2–5 years of age, after adjustments – odds ratio of changing quartiles of weight gain was 4.51 and 4.22, respectively [20].

For other outcomes different from obesity, some lines of evidence suggest another age range. A Chilean study analyzed a population representative sample of 314 children which were born within the normal birthweight range. It was found that changes in BMI, particularly from 6 to 24 months, predicted a higher prevalence of CVD risk at age 4 years. The authors recognized that the presence of CVD biomarkers could either be due to rapid weight gain or obesity (13% of them were obese and 10% presented central obesity). Both explanations would explain the results [20–22].

Fig. 1. Cumulative incidence of type 2 diabetes in adult life in Finland in relation to age at AR. Adapted from Eriksson [1].
This last observation raises another question: when do these later health outcomes appear? The literature suggests that they start long before adulthood.

A risk of elevated blood pressure was detected early at age 7 in a biracial US cohort of 29,710 children. In this study, catch-up growth was measured according to change in relative weight compared with other children. The association of birthweight, catch-up growth and blood pressure at 7 years was analyzed. Not the small for gestational age children were at great risk for hypertension, but those who had greater changes in weight. An increase in weight z score of 1 SD above the previous weight z score increased the odds for high systolic pressure by 1.65 (birth to 4 months), 1.79 (4 months to 1 year), 1.71 (1–4 years), and 1.94 (4–7 years) [23]. In this sense, hypertension seems to be associated with rapid weight gain and not to have a critical period, but to increase its risk in a continuous manner.

The rapid weight gain in childhood should become a reason for permanent alertness for pediatricians. A greater concern for doctors and families is normally when the child is located in lower growth percentiles. In this situation,
hypercaloric diets are recommended to provide a quicker catch-up, and reassure all those who take care of the child. We now know the harm of malnutrition, and we are slowly discovering the harm of an excessive weight gain in childhood. We need to find the equilibrium point in the man-environment interaction.

Since Barker’s fetal programming theory, a lot of evidence has been added to the initial epidemiological association between fetal growth and NCD (e.g. epigenetics). However, the translation into benefits for the exposed population is still in the beginning. Future research should be committed with educational programs and preventive actions focusing on better life behavior in childhood, adolescence and pregnancy.

References


Public Policy Implications of Promoting Growth

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Abstract

Translating the new science of growth into constructive policy will not happen naturally. Rather, the emerging science will need to be reframed to address certain core policy requirements. First, the complexity of early genetic and environmental interactions should be respected as their impact may vary in different, real-world settings. Second, the scale of impact is important to gauge as early-life interactions, while real, may not account for a large portion of later outcomes. Third, judgments regarding critical periods and the amenability of early-life influences to later intervention should be made cautiously as the etiologic nature or timing of early-life interactions do not, per se, determine if their life course effects are amenable to later interventions. Fourth, there is a need for incremental efficacy, such that the new science significantly enhances the impact of extant policy-based interventions. Finally, the translation of the new developmental science into policy should be viewed in a historical context and responsive to social and cultural needs. This provides a basis for reframing the new science of growth in a manner that best ensures that the science receives the constructive policy response it so urgently demands.

Although policy can be defined in many ways, it is inherently a pragmatic enterprise, and can be framed as the transformation of societal intent into societal action. For a scientific audience, it would be affirming to suggest that this process of transformation is rooted in scientific discovery, proceeds logically to carefully evaluated pilot programs, and ultimately to broad policy initiatives. The reality of policy development, however, is far more complex and involves the representation of scientific insight in a manner that supports collective action which, at some level, requires consensus, and consensus is not discovered but created.
This discussion does not make sharp distinctions between industrialized and developing countries as such broad categories tend to obscure shared policy challenges and the considerable heterogeneity that exists among low- and mid-income settings. Rather, the primary consideration is the speed of societal change, particularly the dynamics of nutritional status, patterns of growth, and the rise of chronic diseases. Of central concern are rapidly growing rates of obesity and related chronic conditions in societies still plagued by persistently high levels of chronic undernutrition, including stunting, micronutrient deficiencies, and elevated rates of infectious diseases. This juxtaposition of obesity and undernutrition, while increasingly common among many countries undergoing rapid urbanization and social change, presents a dual challenge to policy development. First, policies must be capable of implementing effective strategies to combat both ends of the malnutrition spectrum, a task that likely requires dramatic reframing of traditional nutritional and public health strategies. Second, the juxtaposition of persistent undernutrition and growing rates of obesity also generally occurs in highly stratified societies, which are often characterized by complex political environments.

Over the past two decades, the social fabric of daily life in transitional societies has been dramatically affected by rapid urbanization, shifts in the availability and pricing of nontraditional foods, and expanded access to technology and mass media. These trends have resulted in profound changes in patterns of consumption such that traditional diets and work-related exercise have been replaced by calorie-dense, nutrient-poor foods and largely sedentary lifestyles. As a consequence, these societies have experienced a dramatic increase in rates of obesity and associated conditions, including diabetes and cardiovascular disease. It is possible that in some settings the juxtaposition of undernutrition and obesity represents only a transitional period in which undernutrition is ultimately replaced by overnutrition and obesity. However, there are troubling signs that undernutrition is not in fact declining rapidly but is stagnating at disturbingly high levels or falling far more slowly than obesity rates are growing.

Recent evidence has underscored the deeper concern that early undernutrition can predispose populations to later obesity in settings of major changes in dietary and activity patterns. It seems clear that undernutrition during gestation and in early life can have long-term consequences for adult health. The concern is that these early exposures to undernutrition create metabolic states that can generate later rapid weight gain in high caloric environments, like those associated with rapid urbanization. This erroneous anticipation of a later nutritional environment has been cogently described as a kind of ‘mismatch’ between early adaptive mechanisms and a later obesogenic environment, and reflects a more general awareness of the developmental origins of health and disease. Although the precise mechanisms driving these relationships remain relatively unexplored, it is likely that they involve complex gene-environment interactions, including epigenetic pathways. In this manner, rather than representing two
distinct nutritional problems, undernutrition and obesity could be intimately related and reflect merely two diverse manifestations of a linked continuum of malnutrition states.

The challenge to policy therefore, must not only address both undernutrition and overnutrition but also respond to the rapidly emerging science that binds them together. There can be no doubt that these scientific insights into human growth and development have been remarkable and are leading to a variety of new directions for research. However, this science is also decidedly complex and may not translate well to the policy arena. Indeed, while the role of early exposures should not be underestimated, this role can also be misinterpreted, and without some caution can ultimately undermine constructive frameworks of clinical and policy-based interventions. This discussion therefore, is not intended as a comprehensive review of the many policy options available to address recent trends in nutrition and health. Rather, it is directed at critically assessing those elements of recent growth and nutrition science that demand special attention in formulating a set of constructive and pragmatic public policies.

Complexity and Norms of Reaction

While a variety of studies have documented associations between early nutritional exposures and later health outcomes, the nature and intensity of these relationships is highly complex and not likely to conform to any singular finding. The clinical or phenotypic expression of any genetic or epigenetic influence can vary profoundly under different environmental exposures. These patterns of variation, or ‘norms of reaction’, can be quite dramatic, changing a given influence from beneficial to deleterious at different levels of given exposure [1, 2]. Because it is very difficult to assess these patterns in real-world settings, great care should be taken in interpreting analyses that assess main or ‘average’ effects of any particular predisposition on later outcomes. Nonlinear or crossover patterns may make average or main effects misleading and render any findings generated under one set of exposures difficult to extrapolate to others. Findings dominated by small changes around the mean may say little about the impact of more extreme exposures. Similarly, experiences at the margins of risk, such as for severely starved infants, may not provide much insight into risk-outcome relationships occurring in the mainstream of exposures. Such nonlinear relationships may also extend to proxy linkages among important, policy-relevant variables. For example, linear growth in small children has been used as a proxy for other outcomes that are more difficult to measure, such as cognitive capabilities. However, these proxy relationships should be viewed as potentially elastic over a spectrum of exposures, such that cognitive effects may be more tightly tied to linear growth at the extremes. This complexity may be
even more apparent when risk-phenotype relationships differ at distinct developmental stages. More broadly, a reliance on statistical strategies based on the analysis of variance may be poorly suited to convey the strength or complexity of gene-environment interactions, particularly if norms of reaction are highly nonlinear or are operating in highly dynamic environments. Overall, the complexity of these relationships suggests that any responsive policy initiative should be fairly comprehensive in its approach and be directed to interventions likely to enhance outcomes over a range of exposures.

**Predictive Utility and the Scale of Impact**

While a number of studies have documented statistically significant associations between early exposures and later health outcomes, policy requires that the scale of these relationships attain public relevance. The basis of such public relevance can take several forms, but generally relates to the prevalence or predictive utility of the relationship in the general population. There may be a variety of significant associations, often viewed as relative risks, for a particular outcome. However, it is quite common for such risks to occur relatively rarely in large populations. For example, adolescent childbearing has been shown to be associated with an elevated risk for infant mortality in the offspring. However, the elimination of the risk associated with adolescent pregnancy would not have a substantial impact on general infant mortality rates as such pregnancies account for a relatively small portion of all births in most populations [3]. There are many justifications for policies designed to reduce adolescent pregnancies; however, the reduction of infant mortality rates is not one of them. While the relative risk was significant, the prevalence-sensitive ‘attributable risk’ was small.

In addition to the attributable scale of an early developmental process, policy must critically consider the predictive utility of identified risk, an issue that is also sensitive to the prevalence of the risk in question. A significant relative risk does not mean that the risk is highly predictive or deterministic of later outcomes. For example, while obesity in 3-year-olds is associated with an elevated risk of obesity as a young adult, the vast majority of obese 3-year-olds are not going to be obese young adults and the vast majority of obese young adults were not obese at the age of 3 years. Indeed, while important recent evidence has emerged suggesting that early developmental processes may prove substantially predictive of a major adult-onset disease process [4], many examined early risks for adult-onset diseases, while real, have not proven to be highly predictive of these later outcomes [5]. Intense interaction with other influences or the likelihood that the outcome in question may represent a condition with heterogeneous etiologic pathways can also undermine the predictive utility of an early developmental risk and therefore, reduce its relevance to policy and public action.
Amenability to Intervention

Policy is concerned with public action, and therefore requires some perception that a capacity exists to actually improve outcomes. Without a belief in the efficacy of a particular intervention, there will be little justification for strong public action. This is why advocacy for a particular intervention or service is always tied to perceptions of efficacy. In the case of early influences on growth and adult health, the appraisal of efficacy takes on a decidedly developmental character. Inherent in arguments that longstanding or permanent risks are determined during confined ages or developmental periods can imply that windows of efficacy are opening and closing during different developmental stages. This notion of confined efficacy is a critical challenge to policy and should, therefore, be examined in detail.

It is useful to note that the nature of a risk, be it genetic, epigenetic, or environmental, has little to do with its relative amenability to intervention. Genetic diseases, such as phenylketonuria, are highly amenable to effective intervention. Similarly, outcomes generally attributed to environmental determinants, such as injuries, are also highly amenable to both preventive and therapeutic interventions. Conditions likely caused by complex gene-environment interactions, such as asthma or type 2 diabetes, are also highly responsive to effective interventions. The concern for policy is whether an efficacious intervention exists, not the nature of the causal pathway per se.

The central focus on amenability also raises questions regarding the invocation of ‘critical periods’ in the generation of life course risk. These developmental stages are generally defined as having increased sensitivity to biologic and environmental influences that result in permanent physiologic or anatomic alterations capable of influencing later health and behavior [6]. However, while such developmental windows of differential sensitivity may exist, there is no reason to believe that their ultimate impact on outcomes is inherently less amenable to intervention than any other category of influence. Experiments by Meaney and Szyf [7] have documented in rats that maternal nurturing practices occurring at a particular time in early development can influence later behavior in offspring through epigenetic mechanisms. However, they have also been able to reverse these effects through the administration of pharmaceuticals [8]. Similarly, from a policy perspective, the advent of human growth hormone treatment has forced a reconsideration of the longstanding perception of critical periods in linear growth. Drugs are merely a manipulated environment and therefore, these illustrations represent examples of a later environmental influence on what had previously been considered fixed outcomes generated by a confined critical period. Sensitive or critical periods, though at some level rooted in developmental processes, are, for the purposes of policy, actually dependent upon whether a later influence or efficacious intervention exists. In this manner, notions of critical periods must be seen as inherently contingent and potentially
dynamic not because of underlying developmental processes but because these processes may be sensitive to the new, efficacious interventions [9]. It may be argued that certain developmental processes or outcomes are better prevented than addressed after the fact. This, indeed, may be true in many current circumstances. However, such an argument is inherently pragmatic in nature, reflecting what is actually a comparative effectiveness logic that assesses the relative utility of different intervention strategies. This approach can be addressed empirically and in the end has little to do with the nature of the underlying developmental processes per se. Policy is dependent on perceptions of capacity, and great care should be exercised when such capacity is challenged on principle. A more useful approach would be to assess such concerns empirically and recognize that during a period of unprecedented growth in clinical and public health efficacy, the policy-based opportunities for effective intervention are likely to be highly dynamic.

**Constructing a Policy Response**

The recognition that the risks associated with early exposures can be complex, highly interactive and potentially amenable to intervention provides a useful foundation for constructing an effective policy response to the undernutrition and growing rates of obesity. For the purposes of this discussion, the components of such a policy response can be considered in relation to three highly interactive components of policy: knowledge base, social strategy, and political will [10].

**Enhancing the Knowledge Base**

While early exposures have been shown to influence later outcomes, there is an urgent need to expand applied research into policies sufficiently comprehensive to address both undernutrition and obesity. Continued investigation of the basic mechanisms involved in early influences on later health remains crucial. Of special concern is the exploration of the complex interactions that persist and reshape life course influences and particularly how efficacious interventions can complement each other at different ages and developmental stages [11]. However, these should be matched by efforts to craft new, innovative strategies to address what is already known to be highly detrimental rates of early undernutrition and elevated child mortality. These broad approaches could include research into larger societal policies, such as those affecting food security or patterns of consumption, as well as more direct, community-based nutrition and health interventions should receive enhanced attention from the research community.
Crafting Social Strategies

Knowledge alone is insufficient for successful policy. Social strategies that attend to prevailing ideologies and the machinery of policy implementation are also essential. In addition, these strategic considerations must respond to programmatic histories, extant funding mechanisms, and systems of provision and accountability. In this manner, policies addressing the continuum of undernutrition and obesity will need to be attentive to the mechanisms of social welfare and planned societal change, mechanisms that may be intensely local and at times, highly flexible, as the parameters of social strategies can change rapidly in unstable political settings.

Given this policy context, the science of malnutrition as well as an examination of prevailing social strategies together underscore the importance of optimizing the health and well-being of women. A traditionally confined focus on the prenatal period does not respond to the longstanding determinants of a healthy pregnancy nor the programmatic requirements of embedding prenatal care within a comprehensive system of women’s health care [3]. Although there are a variety of strategies that hold promise in addressing the nutritional needs of both high- and low-income societies, the importance of healthy childbearing, optimal child nutrition and the shaping of the developmental precursors of lifelong healthy behaviors are in many respects, best addressed by a strong commitment to the health, education, and civic engagement of women. The growing adoption of conditional cash transfer programs in many mid- and low-income countries could also be used more effectively as a basis for improving nutrition. Social strategies that attempt to shift social norms through education, controls on advertising harmful foods, and enhancing healthy behaviors through social and popular media have also been implemented to address other public health challenges, such as tobacco use, and therefore could prove useful in improving general levels of nutrition. It is always important to relate the requirements of optimal growth and development to policies directed at eliminating poverty and enhancing societal equity.

Building Political Will

At some level, all policies must enjoy sufficient political support to ensure their implementation and maintenance. This will often require not only public awareness of the issue but also a political framing that generates sufficient consensus to permit enactment and the appropriation of adequate resources. Particularly in settings of profound social inequity as well as in areas of inadequate or unstable governance, political considerations will prove critically important to effective policy. In this regard, integrated approaches that incorporate developmental science into broader discussions of public health, food economics and policy
should be welcomed [12–14]. However, in calling attention to early influences on later health, great care should be taken not to overextend the claims of early developmental processes and devalue exposures and interventions occurring later in childhood and beyond. Elevating early influence by suggesting that later health outcomes and capacities are merely the product of ‘trajectories’ determined in early life can create unhelpful political dynamics that fragment constituencies and their advocacy. Particularly because the science of life course malnutrition and the relevant social strategies may suggest policies that do not focus exclusively on pregnancy and young childhood (e.g. women’s health), an integrated, comprehensive framework will not only respect the complementarity of interventions and policies over the life course but will also create the coherent, unified political voice that will best ensure the implementation of effective public policy.

References

Pharmacological Interventions for Short Stature: Pros and Cons

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Abstract
Although growth hormone (GH) therapy is virtually always effective in accelerating growth and restoring height potential to children with GH deficiency (GHD), the expansion of its use to a wide variety of other clinical disorders associated with short stature has resulted in considerable ethical and cost-benefit issues. Logic would demand that therapy should either be restricted to true ‘replacement’, thereby limiting its use to cases of unequivocal GHD, or treatment should be considered as a legitimate ‘enhancement’, and be available to all children with significant short stature. Consideration of the latter option requires a careful look at issues surrounding efficacy (both in terms of stature and any perceived disability resulting therefrom), cost and potential adverse effects. Similar concerns involve treatment with insulin-like growth factor-I and any related growth-augmenting therapy. To date, safety issues have been addressed through pharmaceutical-sponsored postmarketing surveillance studies. While of definite use, such investigations also have significant limitations, especially in addressing long-term concerns. The possibility of lifespan cohort studies, with surveillance of all GH recipients throughout life and comparison with data from appropriate controls, should be considered.

In 1926, the distinguished evolutionary biologist, J.B.S. Haldane, published a famous essay, ‘On Being the Right Size’, in which he wryly commented on some of the physical constraints that limit the size of organisms living on Earth: ‘For every type of animal there is a most convenient size, and a large change in size inevitably carries with it a change in form [1]’. As an example, Haldane imagined...
a man 60 feet tall. Such an individual, if proportionate, would also be ten times as wide and ten times as thick as a normal-statured man, resulting in a 1,000-fold increase in mass. Every cross-sectional inch of leg bone would thus need to bear a 10-fold greater weight than normal human bone, and would, inevitably collapse (this is why the legs of elephants are so thick). Additional problems faced by such a tall individual include: (1) a need to pump blood to greater heights, requiring a larger heart, higher blood pressure, tougher blood vessels; (2) greater musculature to manipulate this 1,000-fold increase in mass; (3) an enormous increase in food and energy to support the required metabolism, and (4) a digestive system that could facilitate the necessary caloric requirements for such a great mass.

The principles of natural selection dictate that growth and form evolve so as to best promote the survival of the species and the transmission of its genome to the next generation. As Alfred Wallace wrote: ‘...necessary deduction from the theory of Natural selection, namely – that none of the definite facts of organic nature, no special organ, no characteristic form or marking, no peculiarities of instinct or of habit, no relations between species or between groups of species, can exist but which must now be, or once have been, useful to the individuals or races which possess them [2]’. In that context, it is of note that human growth velocity curves, at least as they relate to Homo sapiens, are characterized by several features which distinguish them from those of other species and which, presumably were 'selected' to maximize survival and reproductive capacity of our species: (1) maximal growth rate is during gestation; (2) birth is followed by a period of deceleration; (3) late sexual maturation (and epiphyseal fusion); (4) occurrence of puberty at the time of the slowest growth rate; (5) an adolescent growth spurt [3]. Of special note is the existence of an adolescent spurt in stature, essentially without parallel in other species, including primates, as well as a relative lack of sexual dimorphism in stature [4, 5]. Indeed, males and females are essentially of identical height prior to the onset of puberty, and the mean difference in adult stature of 12.6 cm between men and women can be virtually entirely ascribed to differential growth during puberty and the timing of epiphyseal fusion [6].

It is, thus, apparent that evolution, acting through natural selection, dictated patterns of fetal and postnatal growth that best suited H. sapiens as a species, including our need to accommodate and deliver a large fetal head, descend from an arboreal pattern of life, assume an upright posture for locomotion, and maintain arms and hands as free as locomotion would permit. When health and nutrition are not limiting factors, the growth patterns and adult heights achieved by humans are remarkably constrained, as evidenced by the relatively limited variation in adult stature for both males and females. It is against this background that pharmacological intervention to alter growth patterns and adult height must be considered.
The Growth Hormone Era

The only growth hormone (GH) that works in man is that derived from humans (or, potentially, other primates). The initial source of human GH (hGH) was from cadaver pituitary glands, requiring laborious and expensive collection of glands, followed by extraction and purification of hormone. The constrained supply limited its use to children with severe GHD, at restricted dosages and suboptimal schedules. With the approval of recombinant DNA-derived hGH, however, the potential emerged for essentially limitless supplies of hormone. Initial approval for treatment of children with GHD was followed, in short order, by approval for therapy for a large number of childhood conditions characterized by short stature, including Turner syndrome, renal failure, Prader-Willi syndrome, small for gestational age (SGA), SHOX deficiency, etc. (see table 1) [7].

The diagnosis of childhood GHD is often difficult, as GH is normally secreted by the pituitary in a pulsatile manner, with serum concentrations throughout the day often being quite low, interspersed with 6–8 spikes of secretory activity. The diagnosis of childhood GHD thus requires, in addition to characteristic growth patterns, demonstration that the patient fails to raise serum GH concentrations following pharmacological stimulation with a number of GH secretagogues. Such tests utilize nonphysiological stimuli and an arbitrary ‘cutoff’ level for peak serum GH, commonly set at 7 or 10 ng/ml. Given the frequent difficulty in establishing an absolute diagnosis, these criteria were constructed so as to avoid excluding a GHD child from receiving therapy, knowingly accepting the fact that treatment might be extended to some children without true GHD. Indeed, it is probable that the majority of children treated for GHD do not have any true GH secretory defect at all. While it is possible that GHD may represent a continuum of GH secretory defects, ranging from absolute to partial deficiency, establishing a diagnosis of GHD remains challenging, especially when the deficiency is not complete. In studies of responsiveness to GH therapy, children with peak provocative serum GH concentrations ≤2 ng/ml tend to grow better than children with higher peak GH levels, but the correlation

Table 1. FDA-approved uses of GH for promotion of height

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<tr>
<th>Condition</th>
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<tr>
<td>GHD of childhood</td>
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<tr>
<td>Turner syndrome</td>
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<td>SHOX deficiency</td>
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<td>Chronic renal failure associated with short stature</td>
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<td>SGA associated with short stature</td>
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<td>Prader-Willi syndrome</td>
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<tr>
<td>Noonan syndrome</td>
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<td>ISS</td>
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Treatment of Short Stature: Pros and Cons 209
between peak GH levels and GH responsiveness is modest, at best, and virtually nonexistent with peak GH levels >2 ng/ml [8].

This issue was either resolved or rendered even more complicated by the approval by the FDA for GH treatment of ‘idiopathic short stature’ (ISS), defined as a height ≤–2.25 SD for age, with normal GH secretion and the absence of other known etiologies for growth failure. In essence, this approval resulted in rendering controversies concerning the diagnosis of GHD moot, since children who did not meet any set of arbitrary criteria for the diagnosis of GHD, could still potentially qualify for therapy under the diagnostic category of ISS. Indeed, in many cases, the deciding factor in the diagnostic categorization of a specific child was not identification of a specific etiology, but, rather, what diagnosis would be reimbursed by the patient’s insurance.

Ethical issues surrounding the use of GH for treatment of short children are, inevitably, complicated by: (1) the cost of treatment, which can range from USD 10,000 to 35,000 per year of treatment; (2) the variability in the growth response, due, at least in part, to the wide range of pathological conditions currently receiving treatment with GH; (3) the complex question of whether short stature, in and of itself, represents a disability, either in childhood or in adult life; and (4) potential adverse effects related to treatment. These are weighty questions and do not lend themselves to simple answers. At the very least, however, children currently receiving therapy for growth failure can be divided into three categories:
1. Children with unequivocal GHD, for whom GH treatment represents true ‘replacement’ therapy. In the overwhelming majority of such cases, if GH therapy is begun at an early age and administered at a proper dosage, the child can attain his genetic target height.
2. Children with underlying medical conditions, in which growth failure is a common feature, but not ascribable to defects of GH production. Such conditions include Turner syndrome, SHOX deficiency, chronic renal failure, and Prader-Willi syndrome (although some of the latter group may also have abnormal GH secretion). In such cases, GH therapy is not designed to replace a deficiency, but, rather, to override the underlying growth pathology by administering superphysiological levels of GH and, possibly, insulin-like growth factor-I (IGF-I). In general, such children show a partial response to GH therapy, accelerating growth, exceeding their otherwise destined adult stature, often achieving adult heights within the lower part of the normal range, but not attaining their full genetic target heights. To the conditions listed above, one might add a variety of chronic medical conditions frequently characterized by growth attenuation, such as inflammatory bowel disease, cystic fibrosis, chronic steroid use, etc., in which definitive data on improved growth are currently still unavailable.
3. Children in whom no underlying pathology, either endocrine or nonendocrine, can be demonstrated, but who are, nevertheless short. Some
of these children are simply constitutionally delayed and will, in time, have a late, but otherwise normal pubertal growth acceleration and attain normal adult stature without pharmacological intervention; these patients should not, in general, be considered suitable candidates for GH therapy. Other cases fall into the broad diagnostic category of ISS and, potentially, qualify for therapy with GH. A subset of ISS patients with severely low serum IGF-I concentrations despite normal GH secretion may be labeled as ‘severe primary IGF deficiency’ (IGFD) and qualify for treatment with IGF-I, although long-term data are still unavailable, except for patients with severe GH resistance [9]. Children born SGA and who fail to return to the normal range (i.e. >–2 SD) by age 2–4 years of age are also candidates for GH therapy.

In reviewing these categories, it becomes apparent that logic would dictate two potential approaches: (1) sharply limit GH treatment to children with unequivocal GHD, in whom treatment represents true replacement [the same may be true for IGF-I treatment of rare cases of severe GH resistance, resulting from mutations of the genes for the GH receptor (GHR), signal transducer and activator of transcription 5b (STAT5b), or IGF-I (IGF1)]; or (2) consider growth failure and short stature a ‘disability’, and make therapy available to all children meeting an arbitrary definition of short stature, regardless of the underlying etiology.

The ethical issues involved in choosing between these approaches have been well-summarized in a series of papers by David Allen and colleagues [10, 11]. An important factor lies in the definition of ‘disability’, and whether therapy represents ‘treatment’, or merely ‘enhancement’. Despite extensive anecdotal experience, as related by patients, parents and health care providers, there is little in the way of long-term controlled studies supporting the belief that such therapy provides clinically significant psychological or social benefit [12].

On the other hand, from the perspective of the small child, the etiology of the short stature is largely irrelevant. If the child perceives himself to be disadvantaged by his/her stature, it is of little importance whether GH treatment constitutes replacement of a deficiency or not. If, then, one argues that the etiology of the growth failure is not a critical issue, the key questions largely resolve into ones of efficacy, cost and safety.

**Efficacy**

As stated above, for the child with true GHD, GH therapy, if initiated at an early enough age, at a proper dosage and for a sufficient period of time before epiphyseal fusion occurs, can, typically, restore the child to his full genetic potential, in terms of stature. In the case of IGF-I treatment of severe primary IGFD, even in the most ‘classical’ cases, such as mutations of GHR, growth acceleration does
occur, but the degree of catch-up growth does not duplicate that observed with GH treatment of GHD, and few patients attain their full genetic target height. Nevertheless, the value of GH or IGF-I treatment, respectively, in unequivocal GHD or severe primary IGFD resulting from GHR defects, is unequivocal [7, 9].

For many of the other conditions currently treated, including FDA-approved indications, the long-term benefit is somewhat less certain. Data from multiple clinical trials in Turner syndrome and ISS indicate that GH therapy increases growth rate and adult height. For many patients, especially when treatment is initiated early in life at an adequate dosage, heights within the normal range for adult stature are attainable. On the other hand, larger dosages of GH are generally required than is true for GHD, the growth acceleration is more modest, and full attainment of genetic target height is often not possible.

Cost

The cost of GH or IGF-I is dosage-related, but, annual costs of USD 15,000–35,000 are fairly typical. In a child with GHD diagnosed at the age of 2 years, therapy would be continued until epiphyseal fusion, necessitating 10–15 years of treatment (not to mention the continued cost of lower dose GH therapy during adult life). For many of the other conditions commonly treated, relatively long-term treatment (usually at least 4+ years) is necessary to see the more modest improvement typically observed for these disorders. If one were to consider treatment for all children with heights <−2.25 SD (the current FDA-approved criterion for ISS) in the United States (~75,000,000 population <17 years of age), therapy would be required for ~900,000 patients. At an average annual cost of USD 20,000 per patient, this generates a total of USD 18 billion/year. Obviously, not all short children between birth and 17 years of age would be treated, and not for every one of their first 17 years of life, so this astronomical number requires serious adjustment. Nevertheless, an annual cost of USD 1.6–4 billion has been provided as a reasonable estimate of potential cost of treatment for short stature in the United States alone [10]. Whether such costs would be reimbursed by insurance is beyond the point, as this expenditure would have to come from somewhere in the healthcare budget.

Central to the issue of cost is the duration of treatment, which, at least in part, depends upon the ultimate goal of therapy, a matter for which no objective criteria have been identified. Should treatment continue until the child achieves a height within the broad ‘normal range’ (i.e. >−2 SD), or until he/she attains the mean stature for sex, or the parental genetic target height, or, perhaps, the height desired by the patient and family? And, of course, every time a short child is moved into the normal range, another child falls out of the normal range. It is, obviously, impossible for every individual to be between ±2 SD, just as it is impossible for every wage-earner to have an income above the national average.
Safety

The era of pituitary-derived GH ended in the early 1980s when it was shown to be associated with Creutzfeldt-Jakob disease, a devastating and lethal neurodegenerative disorder. rhGH has been in use now for over 25 years and has an enviable track record of safety. To date, most safety data derive from pharmaceutical company-sponsored postmarketing surveillance studies, which have reported findings in ~200,000 patients and >500,000 patient-years. Many of the GH-associated adverse effects have been related to rapid growth, such as progression of scoliosis or slipped capital femoral epiphyses. Others, such as increased intracranial pressure, are occasionally observed with a variety of hormone replacement therapies. Hyperglycemia and exacerbation of preexisting diabetes mellitus are rare, but not unanticipated consequences of GH treatment, given the known insulin antagonistic actions of GH. Recently, the long-term safety of rhGH was evaluated in almost 55,000 patients enrolled in the National Cooperative Growth Study, through the reporting of adverse events by prescribing physicians [13]. Nineteen of 174 deaths were considered by the physicians to be related to rhGH, although an additional 25 deaths were labeled as ‘non-assessable’ or had no reported causality. Although 2/3 of the assessable deaths were related to neoplasia, the authors concluded that the findings support a ‘favorable overall safety profile’.

It is necessary to point out that, despite the clear value of such postmarketing survey studies, they are characterized by a number of significant limitations: (1) reliance upon physician reporting of adverse events, as well as physician assessment as to whether such events are ‘GH related’; (2) incomplete enrollment of patients in such studies, with great variation in drug exposure and compliance with treatment regimens; (3) studies are time limited and are not necessarily designed for thorough follow-up of patients after treatment has ceased; (4) absence of any kind of suitable control group; (5) studies are under the supervision of the sponsoring pharmaceutical company, which control access, analysis and release of data, and (6) a lack of collaboration among the various postmarketing studies.

The issue of GH and/or IGF-related neoplasia has been a persistent concern, in light of substantial evidence supporting the involvement of the GH-IGF axis in the pathogenesis and progression of a variety of cancers [14–16]. Both GH and IGF receptors have been identified in cells from multiple forms of cancer, and both hormones have been shown, at least in cell culture and animal explant studies, to have potent mitogenic and proapoptotic actions. In a wide variety of animal models, manipulation of various genes involved in GH and IGF secretion and action have been shown to influence the occurrence or progression of cancers. Human epidemiological data are, at least to date, less convincing, although a recent report suggested that patients with GHR defects have a dramatic reduction in cancer frequency [17]. In a series of nested case-control
studies, a correlation has been reported between serum IGF-I concentrations in normal individuals and cancer risk. Although the conclusions of such studies are not always consistent, a recent meta-analysis of 26 investigations calculated the cancer risk at the upper quartile of serum IGF-I to be approximately 1.5 times that at the lowest quartile [18].

While studies of the risk of tumor recurrence in patients receiving GH therapy have been reassuring, some studies have suggested an increase in the frequency of second neoplasms in GH-treated cancer survivors [19]. Although these conclusions remain controversial, they serve to underscore the concern about a potential relationship between GH or IGF-I therapy and neoplasia, either primary or recurrent [20].

In late 2010, Agence Française de Sécurité Sanitaire des Produits de Santé issued a preliminary report concerning the findings of a long-term morbidity and mortality study [21, 22]. The French SAGhE (Santé Adulte GH Enfant) is part of a multinational European consortium, involving seven countries and entitled SAGhE (Safety and Appropriateness of GH Treatments in Europe); it is not clear why the French investigators elected to release the findings of their study separate from those of their collaborators [23]. In any case, the French investigation was based upon a mandatory registry of all patients treated with rhGH in France from the time of its introduction in the mid-1980s until 1997, encompassing approximately 7,000 patients carrying the diagnosis of idiopathic GHD, ISS or SGA, with a mean follow-up time of 16.9 years. For obvious reasons, an identical population of untreated children with these diagnoses was not available, and for comparison purposes, an age-specific French population was employed.

While the French report has yet to be published at this time, the results have been presented at a variety of national and international conferences. In the GH recipient group, 93 deaths were recorded, compared to an expected 70, yielding a standardized mortality rate (SMR) of 1.33. The total number of cancer deaths in the two groups was identical, although the investigators have emphasized an increase in bone-related cancer (3 cases vs. an anticipated 0.6). The greatest identifiable discrepancy between the two groups was in deaths related to ‘circulatory system’ disorders, where 9 were observed, compared to an anticipated 2.93, yielding an SMR of 3.07.

On the basis of these findings, the European Medicines Agency Committee for Medicinal Products for Human Use issued a statement of ‘no immediate danger’, but instructed prescribers to strictly follow approved indications and dosage. No critical evaluation of the findings was provided. Unfortunately, the French SAGhE study, which is to be commended for initiating and conducting an important investigation, is characterized by a number of significant weaknesses and limitations which should be identified and discussed in an open scientific atmosphere [24]. These limitations include, but are not limited to: (1) lack of a suitable control population; (2) failure to emphasize that conditions
such as idiopathic GHD, ISS and SGA may, in and of themselves, carry significant morbidities and may be characterized by unrecognized molecular and biochemical abnormalities; (3) failure to fully characterize a number of deaths labeled as ‘idiopathic’ or non-assessable, because no cause of death was recorded on the death certificate, and (4) questionable statistical evaluation of a number of the recorded morbidities and causes of death.

Conclusions

The use of agents such as GH and IGF-I as replacement treatment to accelerate growth and improve adult stature appears fully justified in conditions where therapy replaces an unequivocal deficiency, as is the case for GH treatment of GHD and IGF-I therapy for severe primary IGFD, where serum IGF-I cannot be raised through alternative means. Therapy with these agents in conditions where growth failure cannot be directly ascribed to a deficiency of the respective hormone is a more difficult issue, involving distinguishing between ‘treatment’ and ‘enhancement’, and weighing any perceived benefit against potential adverse effects and cost to the healthcare system.

As stated above, rhGH has had an excellent record of safety. Long-term experience with IGF-I is much less extensive, although no unexpected adverse events have been identified to date. It must be recognized, however, that even when therapy is directed at treatment of the cognate hormonal deficiency, the underlying disorder is not life threatening and that long-term adverse effects of treatment, even if only theoretical, must be considered. Postmarketing studies sponsored by the pharmaceutical industry, while of value, cannot be relied upon as the final arbiters of long-term safety. The SAGhE studies, including the French and other European investigations, represent an excellent effort to perform the necessary surveillance free of industrial oversight or interference, but have their own inherent limitations; furthermore, no similar studies have been undertaken within the United States.

In a recent publication in The Journal of Clinical Endocrinology and Metabolism, it was recommended that the endocrine community should endorse investigations of GH and IGF-I safety through establishment and follow-up of lifespan cohorts consisting of patients treated with GH or IGF-I during childhood, adolescence and adult life [24]. It was proposed that all GH/IGF-I recipients be included, regardless of underlying diagnosis. Such studies would be independent of commercial control, and instead be supervised by an independent, multidisciplinary investigative team with appropriate expertise and experience to assume primary oversight and conduct of a lifespan cohort.

This is, obviously, a highly ambitious undertaking, and pilot studies would be required to determine the feasibility of both retrospective and prospective enrollment, the appropriate mechanisms of follow-up, and the resources required for
initiation and maintenance of a lifespan cohort. Consideration must be given to issues such as sample size, statistical power, diagnostic categorization, sociodemographics, capacity to achieve comprehensive long-term surveillance, and the composition of the most appropriate control group(s). Despite these difficulties, lifespan cohorts have proven to be invaluable in assessment of risk/benefit of other treatment modalities, most notably chemotherapy in childhood cancer [25]. Without responsible data on long-term safety of growth-promoting agents, it is still impossible to provide any definitive assessment of the pros and cons of such therapy.

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Discussion on Childhood Growth and Later Outcomes, Policy Implications and Treatment of Short Stature

This session focused on three presentations, all addressing the question of identification, consequences, and interventions around child growth. Child growth is the result of interactions between the child’s genotype and environment, broadly defined. We study growth because it is an indicator of the outcomes of these interactions, but primarily because it is an easily recognizable (and measurable) phenotype. Variation in attained height has cultural meaning – being shorter than average has adverse consequences for economic productivity, and because men tend to marry women shorter than they are, shorter men have a more limited marriage market. Dr. Rosenfeld described the specific circumstances of severe growth retardation and role of recombinant growth hormone in its treatment. Dr. Ferraro highlighted several clinical consequences of variation in growth. For all these reasons, there is intense legitimate interest in identifying the underlying determinants of attained size. Dr. Wise discussed the underpinnings of public health policy, and the need to translate research findings to a wider audience.

A big advance in the study of growth and its determinants and consequences has been the development of an international growth standard, based on the growth pattern through age 5 years of singleton term children born to upper middle-class non-smoking women who planned to breastfeed their child according to current recommendations [1]. What becomes clear from these data is that once socioeconomic constraints on growth and variations attributable to infant feeding patterns are controlled, children grow, on average, at similar rates around the world. This has major implications for screening, research and policy. Now that we know how normal, healthy children do grow, we can move to discussions of whether deviations from this pattern have significance.
Extreme growth failure is rare and may require therapeutic intervention. Dr. Rosenfeld spoke of the therapeutic efficacy of recombinant growth hormone, highlighting the very narrow clinical usages where it is highly efficacious, and the lowered efficacy in settings where growth hormone deficiency is not the primary cause. This has lessons for the community of researchers and practitioners who see variation in growth in the normal range, or who see widespread levels of growth retardation that result from frank undernutrition. Dr. Rosenfeld highlighted that one indication for growth hormone replacement therapy is a height >2.25 SDs below the reference. In Guatemala and elsewhere, close to half the population would meet this criterion [2].

One area of growth research that is not yet understood is the adiposity rebound. Children’s BMI trajectory shows a nadir. It has been shown in multiple settings that the age at which this nadir appears varies across individuals (from as low as 3 years to 10), and that the age at the nadir is associated with a higher BMI percentile, such that children with a higher BMI early in life experience an early nadir, and children who experience an early nadir have a greater increase in their subsequent BMI [3]. However, nothing is known about our ability to intervene and affect the age or the level of the adiposity rebound, so the relevance of the adiposity rebound beyond being a marker of risk is yet to be determined.

This brings us to the question of policy around growth. Effective public health policy, as described by Dr. Wise, requires a solid base of high-quality evidence for efficacy, a meaningful target population who will benefit, and a supportive social climate. Dr. Wise highlighted the need to categorize risk factors in terms of both their relative risk and their distribution in the population. At a population level, these two epidemiologic concepts come together as a population-attributable risk; in other words, the extent to which a change in the risk factor would result in a change in the population-wide burden of disease. Policy then becomes a discussion between those who argue for focused interventions with highly efficacious tools targeted at those individuals at elevated risk (which would be appropriate for risks that are narrowly distributed in the population) versus those who argue for population-wide interventions, appropriate when the risk factor is widely dispersed. While either approach requires evidence for efficacy, they will differ in their tolerance for safety. As in clinical medicine, the adverse effects of any intervention need to be outweighed by the effectiveness, but unlike clinical medicine, the adverse events and the effectiveness may happen in different individuals, complicating the discussion.

In this context, one might want to distinguish between ‘healthy’ and ‘healthful’ growth. Healthy growth is a descriptive concept. It might be understood to be growth that tracks along a growth percentile within the normal range, and is consistent with adult functioning within the normal range. Discussion of healthy growth recognizes that variation among individuals is normal, that
much within-individual variation is self-limiting and reflects short-term factors. Healthful growth, on the other hand, is predictive and prescriptive. A model of healthful growth argues that there is an optimal growth pattern, and that any deviation from that pattern will be accompanied by adverse consequences in adult life. The work by Ferraro and others, including myself, who assess the associations between growth in various stages of childhood and adult metabolic disease are firmly located in this latter model. The model has clearly shown that the ‘first 1,000 days’ – the period from conception through the second birthday, is a window in which much development is happening [4]. Studies from Guatemala have shown that a food-based intervention can improve growth, adult cognitive achievement and economic productivity [5–7], providing a strong proof of concept that there is an underlying role of nutrition in early childhood in both growth and adult health and well-being. However, a risk of this model is that investigators and those who interpret their research face the risk of overinterpretation. Accepting the associations as being causal often leads to an assumption that a specific intervention known to affect growth will also impact on the later outcome. Making this leap requires a detailed assessment of the underlying shared pathways – this work is still in its infancy. The study in Guatemala used a micronutrient-fortified complementary weaning food as the intervention. As the control condition provided some calories from sugar in addition to the micronutrients, these data have been interpreted as supporting a role for protein, or for animal-source foods more generally. Other studies have focused on individual micronutrients, including iron, zinc, docosahexaenoic acid – the evidence that they are rate limiting in child growth is limited. As the causes of variation in growth vary across settings and across individuals within particular settings, with the specific rate-limiting factor being unknown in specific settings, moving beyond broad recommendations to feed children a diverse diet may be premature. As Dr. Wise pointed out – often the consensus becomes ‘adolescent girls should eat more vegetables’ – although the evidence that this is in fact efficacious is absent.

_Aryeh D. Stein_

References

Concluding Remarks

The 71st Nestlé Nutrition Institute Workshop consisted of three interdependent sessions regarding nutritional, molecular and endocrine aspects of growth. In the first session, Drivers of Growth, speakers addressed nutritional, genetic, and epigenetic influences on fetal and postnatal gain in linear growth and in markers of adiposity. The presentations in the second session, entitled Secular Trends in Growth, encompassed not only changes over time in parameters of growth, but also evolutionary and economic drivers and consequences, and it involved discussion of developing- as well as developed-country perspectives. The speakers in the third session faced the challenge of addressing What Is Healthy Growth? This session included growth standards, outcomes of early growth in developed and developing countries, policy perspectives regarding promotion of growth, and pharmacologic approaches to short stature.

This workshop was timely, given the pandemic of obesity, which is rapidly emerging throughout the world, and whose roots exist in the earliest stages of development. While weight is the growth parameter most readily available in most countries, it alone is no longer sufficient to characterize growth because it encompasses both linear growth and weight in excess of length (a proxy for adiposity). This principle holds for the prenatal period as well as after birth, and calls for new sources of data to disentangle the two components. This distinction is particularly important in the developing world, in which early linear growth faltering is still common, the dual burden of stunting and overweight exists within communities and even the same family or individual, and wasting is becoming less common. In both developed and developing parts of the world, the first 1,000 days from conception through the first 2 years of life appear to be a window of opportunity for setting children on healthful lifetime trajectories.

As demonstrated in all three sessions of this workshop, the distinction between linear growth and adiposity matters because their nutritional, genetic, epigenetic, economic, and evolutionary determinants are different. Whether the infant is born preterm or at term modifies the impact of these forces. The timing of growth acceleration or faltering partly determines later outcomes.
Trade-offs can exist; for example faster growth in weight-for-length among infants born preterm could enhance cognition at the expense of later adiposity and cardiometabolic risk. Other salient outcomes, such as reproductive fitness and economic productivity, are rare to date in the research literature, but could be critical for understanding early growth indices and thus for mounting interventions. Interventions to promote linear growth without inducing adiposity are needed, but few are currently available except for pharmacologic treatment of short stature, an uncommon situation limited to resource-rich environments. As a consequence, policies to increase weight at birth or in the postnatal period, which have been the mainstay of many public health campaigns, could ultimately backfire in the 21st century as obesity becomes the principal early childhood nutritional menace.

Key research challenges include better characterization of growth trajectories, quantifying modifiable determinants of various aspects of growth that also predict important health outcomes, understanding their genetic and environmental modifiers (including social context), identifying the extent to which critical or sensitive periods exist, and performing intervention studies to improve health and socioeconomic outcomes. The extent to which interventions can be ‘one size fits all’ vs. ‘personalized’ will largely determine how public health policy is created and implemented.

A novel feature of this Nestlé Nutrition Institute Workshop was the assistance of two invited discussants for each of the three sessions. The discussants deftly led the audience and speakers into areas that expanded and extended the speakers’ presentations. In addition to the speakers’ chapters, each discussant has contributed a summary to this book and perusing them is rewarding.

We heartily thank the invited speakers and discussants, as well as the organizers from Nestlé Nutrition Institute, for generating an informative and thought-provoking workshop that will help pave the way for future research and policy in achieving optimal health through modifying early growth.

Matthew W. Gillman
Peter D. Gluckman
Ron G. Rosenfeld
Economic analysis, see Social-economic-political environment; Stunting

Epigenetics
assisted reproductive technology and loss of imprinting 71
critical development periods 60–62, 66
fetal growth modulation 66, 67
height heritability 41, 42
imprinting in disease 55
life course strategies for non-communicable disease prevention and treatment 58, 59
multilocus imprinting disorders 70, 71
RXRA promoter methylation and later obesity risks 60–62
secular change in growth patterns 123–125
syndromes with defects, see Beckwith-Wiedemann syndrome; Russell-Silver syndrome

Evolutionary perspective, growth developmental plasticity 91, 92, 97
gestation length and environmental effects 94
glossary of terms 99, 100
humans versus other animals 208
life history theory 92–95
overview 90, 91
microevolution 90, 91
phenotypic-driven evolution 93
pubertal maturation 96–98

Failure to thrive (FTT) 172, 173
Fetal growth, see also Gestation length
birthweight secular trends
Australia 106
Canada 105
China 106
fetal growth and determinants 109–111
France 105
overview 103, 104
prospects for study 111, 112
United States 104–107

Dutch Winter famine studies 79, 80
energy supplementation optimization 7
epidemiological evidence of early life developmental programming 77
epigenetics studies, see Epigenetics
 genetic regulators 78, 79
glucocorticoids in programming 80
growth hormone regulation 76, 77
macronutrient interventions
 energy decrease 4
 energy increase 2, 3
 protein greater than 25% of energy 3, 4
 protein less than 25% of energy 3
multiple nutrient interventions 6, 7
overview of factors affecting 1, 2
single-nutrient interventions 5, 6
FTO, genome-wide association studies of growth 30–32

Genetic Investigation of Anthropometric Traits (GIANT) 32
Genome-wide association study (GWAS), growth traits
complexity of growth genetics 34
FTO 30–32
HMGA2 31
overview 29, 30
postnatal growth studies 32, 33
prospects for study 34–37
pubertal growth studies 33, 34
sample size increase 31, 32

Gestation length
 environmental effects 94
secular trends 107–109
Glucocorticoids, maternal programming of fetal growth 80
Glucokinase, mutation and fetal growth 78

Growth hormone (GH)
fetal growth regulation 76
genetic defect investigation algorithm 52, 53
insulin-like growth factor-I axis 44, 45
leptin modulation 81, 82
receptor mutations and phenotypes 46–48
therapy
cost 210, 212
efficacy 211, 212
ethics 210, 211
indications 209–211, 220
safety 213–215

Growth standards
historical perspective
child rearing and anthropometry 162, 163
French contributions 164–166
weighing and charting 163, 164
prospects for study 189
universal, provisional standards 168, 169
variability of growth in 20th century 167, 168
World Health Organization charts 161, 162, 169, 185, 186

HMGA2, genome-wide association studies of growth 31

Hypertension
birthweight and childhood body mass index correlation 195
salt intake studies 159
obesity comorbidity in developing countries 150–152

IF1H1, genome-wide association studies of growth 35

Imprinting, see Epigenetics
Infancy-Childhood-Puberty Growth (ICP) Model 12
Infants, see Postnatal growth
Insulin-like growth factor-I (IGF-I)
acid-labile subunit mutations and phenotypes 49, 50, 78
breastfeeding response in infants 20–23
fetal growth regulation 76–78
functional overview 43, 44
 genetic defect investigation algorithm 52, 53
 growth hormone axis 44, 45

Infancy-Childhood-Puberty Growth Model 12
leptin modulation 81, 82
receptor signaling 45
mutations and phenotypes 50, 51
therapy 51, 52, 210–213, 215
Insulin-like growth factor-II (IGF-II), imprinting and fetal growth 67, 79, 80

Intrauterine growth retardation, see Fetal growth

Leptin, growth hormone-insulin-like growth factor modulation 81, 82

Life history theory
evolutionary perspective of growth 92–95
pubertal maturation 96, 97
LIN28B, adolescent growth genome-wide association studies 33, 34

Malnutrition, see Stunting
Mammalian target of rapamycin (mTOR), growth regulation 12, 13

Maya, social-economic-political effects on growth 122, 123
MCR4, growth regulation 34

Non-communicable disease, see specific diseases

Obesity
activity energy expenditure and population weight gain 152–154
comorbidities in developing countries 149–152
coronary heart disease, birthweight, and childhood body mass index correlation 192, 193
critical periods of development 194
energy intake and population weight gain 154, 155
infant diet
breastfeeding protective effects 15–21
energy and later obesity risk 13, 14
leptin and growth hormone-insulin-like growth factor modulation 81, 82
malnutrition and risks 135–137, 143–146
RXRA promoter methylation and later obesity risks 60–62
screening for cardiometabolic disorders 160
Omega-3 fatty acids, fetal growth intervention studies 5, 6
Osteoporosis, childhood weight gain and programming 193

Placental dysfunction, fetal programming 81
Policy, see Public policy
Postnatal growth
animal models 41
breastfeeding protective effects
Early Protein Hypothesis 17–19
infection and diarrhea 14, 15
obesity in later life 15–21
clinical trials
challenges 40
effectiveness 39, 40
end points 40
diet impact on later obesity risk 13, 14
epidemiological evidence of early life developmental programming 77
epigenetics studies, see Epigenetics
genome-wide association studies 32, 33
regulators 12, 13, 40
trade-offs in developed world
full-term infants 172–174
overview 171, 172, 186–188
preterm infants 174–178
prospects for study 180–182, 189
small for gestational age
infants 179, 180
Pregnancy, see Fetal growth; Gestation length
PTPN11, mutations and phenotypes 51
Puberty, see Adolescent growth
Public policy
amenability to intervention 203, 204
complexity of early nutrition and later outcome relationship 201, 202
components of policy response
knowledge base enhancement 204
political will building 205, 206
social strategy 205
overview 199–201
predictive utility and scale of impact 202
Russell-Silver syndrome (RSS)
diagnosis
clinical 68, 69
molecular 69
epimutations 68
genotype/phenotype correlations 69
RXRA, promoter methylation and later obesity risks 60–62
Secular trends, see Adolescent growth;
Adult stature; Childhood growth; Fetal growth; Gestation length
Small for gestational age, see Fetal growth
Social-economic-political (SEP) environment
secular changes in growth 118, 120–122
stunting, see Stunting
STAT5B, mutations and phenotypes 48, 49, 78, 79
Stunting, see also Childhood growth; Fetal growth
malnutrition
income growth role in prevention 134–136
interventions
economic analysis 132, 133, 135
outcome selection 137–140
non-communicable disease risks 135–137, 143–146
synergy between economics and nutrition 133, 134
Trends, see Secular trends
World Health Organization (WHO),
growth charts 161, 162, 169, 185, 186