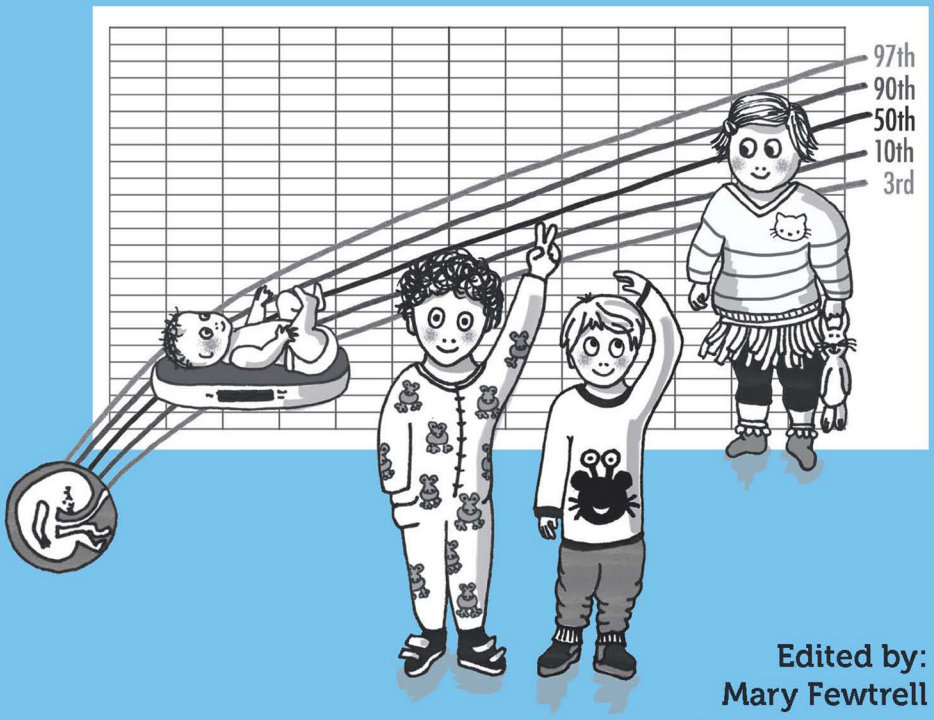
Growth in Early Life:

Growth Trajectory and Assessment, Influencing Factors and Impact of Early Nutrition



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Essential Knowledge Briefings

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Disclaimer

Any information provided herein with regard to the identification, management, and prevention of compromised fetal growth, or growth deviations in infancy and childhood, is intended to serve as a guide only, and should not replace careful diagnostic work-up and appropriate clinical judgment.

Acronyms

AAP	American Academy of Pediatrics
AGA	Appropriate for gestational age
BMI	Body mass index
CDC	Centers for Disease Control
CRH	Corticotrophin-releasing hormone
DOHaD	Developmental Origins of Health and Disease
ECHO	End Childhood Obesity (WHO initiative)
ELBW	Extremely low birth weight
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology, and Nutrition
FGLS	Fetal Growth Longitudinal Study
IGF	Insulin-like growth factor
IOM	Institute of Medicine
IU	International units
IUGR	Intrauterine growth restriction/retardation
LBW	Low birth weight
LGA	Large-for-gestational-age
MGRS	Multicenter Growth Reference Study
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
PUFA	Polyunsaturated fatty acids
SAM	Severe acute malnutrition
SGA	Small-for-gestational-age
VLBW	Very low birth weight
WHA	World Health Assembly
WHO	World Health Organization

Glossary

AGA	Infants born "appropriate for gestational age" are those whose birth weights fall between the 10th and 90th percentiles of the expected weight for their gestational age.
BMI	Body mass index is defined as weight in kilograms divided by height (or length) in meters squared (kg/m^2).
ELBW	Extremely low birth weight (<1,000 grams).
Failure-to-thrive	Also termed "growth faltering". These are pediatric terms used to describe inadequate growth, or the inability to maintain adequate growth. These terms represent a state of under-nutrition, but should not be used as an actual diagnosis.
LBW	Low birth weight (<2,500 grams).
LGA	Large-for-gestational-age infants may be born at term, preterm, or post-term, but with a birth weight greater than the 90th percentile for their gestational age.
Macrosomia	Infants born with an excessive birth weight (>4,000 or >4,500 grams).
Preterm	Preterm infants are defined as those born with a gestational age of <37 weeks.
SGA	Small-for-gestational-age infants may be born either at term or preterm, but have a birth weight lower than the 10th percentile for their gestational age.
Stunting	Refers to poor linear (length or height) growth. The WHO defines stunting as low length-for-age (0-24 months, infancy) or height-for-age (>24 months, childhood), which is greater than two standard deviations below the mean of the WHO growth standards.
Underweight	Low weight-for-age, defined by the WHO as more than two standard deviations below the mean of the WHO growth standards.
VLBW	Very low birth weight (<1,500 grams).
Wasting	The WHO defines wasting as low weight-for-length (infants) or low weight-for-height (children), which is greater than two standard deviations below the mean of the WHO growth standards.

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Chapter 1

Introduction

The growth journey in early life

The first 1,000 days, from conception until the age of two years, comprise a unique period of tremendous physiological growth and rapid functional development of the body's organs. It is during this time that a fetus, infant (<12 months of age) or toddler (1-2 years) is most susceptible to environmental influences that can profoundly affect critical stages of this development process, with subsequent short- and/or long-term consequences for health and physical performance.[1-3]

Along with genetic and physiological factors,[4] environmental factors e.g. poor hygiene, poor maternal or infant nutritional status, disease burden, and low socioeconomic status may adversely influence fetal and/or infant growth and development.[5] Due to the specific nutritional requirements during this period of rapid growth, even small nutritional deficits, especially when persistent, may negatively impact growth, development and later health. Thus, adequate nutrition, particularly during the first 1,000 days – starting with good maternal health and nutrition status during pregnancy, and adequate infant and child nutrition after birth – is one of the fundamental prerequisites for survival, growth, optimal development, and lifelong health.[6-8]

> Adequate nutrition during the first 1,000 days . . . is one of the fundamental prerequisites for survival, growth, optimal development, and lifelong health.

The global burden of malnutrition

At the population level, adequate nutrition during the early years is a pivotal factor influencing societal health, stability, sustainability, prosperity, and long-term population growth.[1,7]

Malnutrition is a growing global concern.[7] UNICEF reported in 2014 that:[3,9,10]

- Approximately 95 million children under the age of 5 years worldwide (approximately 14%) were underweight.
- Around 3 million children die each year from under-nutrition, equating to nearly half of all deaths in this age group. Majority of underweight children live in Southeast Asia and sub-Saharan Africa; in contrast, the prevalence of underweight is only approximately 2.4% in high-income countries.

Over-nutrition, on the other hand, is a growing global issue in low and middle-income countries as well as high-income countries, and is associated with serious long-term adverse consequences. UNICEF data published in 2014 indicated that:

- Approximately 41 million children under 5 years worldwide (7%) were overweight.[3]
- Prevalence of overweight children under 5 years is steadily increasing, expected to reach 64 million (10%) by 2025.[10]

Almost half of all countries around the globe are facing a so-called "double burden" of malnutrition – poor child growth and development and micronutrient deficiencies, as well as increasing overweight and obesity rates within the same population.[7]

Population-based nutrition intervention programs have been shown to significantly reduce the economic and human burden of communicable diseases such as tuberculosis and malaria, and the long-term risk of non-communicable, chronic diseases such as diabetes in adulthood.[1,7,8] While much progress is currently being made, overall global progress remains slow, and is uneven between countries. In particular, the prevalence of overweight and obesity continues to increase, especially in countries undergoing rapid demographic transition.[7,11]

Progress toward WHO Global Targets for 2025

In 2012, WHO's Member States endorsed six key global nutrition targets established by the World Health Assembly (WHA) for improving maternal, infant, and early childhood nutrition by the year 2025 (**Table 1**).[11]

Global progress is currently off-track to achieve these targets but progress continues to be monitored by the WHO, and national plans continue to be implemented (**Table 2**).[7,11]

Established global malnutrition interventions primarily target under-nutrition. However, it is becoming increasingly important to also consider interventions targeting over-nutrition, especially in countries in transition where high rates of both conditions co-exist.[12] This includes populations with historically high rates of under-nutrition that are undergoing rapid socioeconomic development and/or nutritional transitions, placing them at particular risk of obesity increases.[12] One example is Chile, where malnutrition prevalence decreased from 37% to 3% in children under 6 years of age between 1960 and 2000 as a result of demographic and nutritional development, but with a simultaneous increase in childhood obesity that climbed to 20% by 2008.[13] It is thus acknowledged that focusing efforts solely on eliminating under-nutrition in such countries may have unwanted consequences in terms of rising obesity rates. Notably, the

Table 1. WHO Global Nutrition Targets for 2025[11]

1	40% reduction in the number of children under-5 who are stunted
2	50% reduction of anemia in women of reproductive age
3	30% reduction in low birth weight
4	No increase in child overweight
5	Increase the rate of exclusive breastfeeding in the first 6 months up to at least 50%
6	Reduce and maintain the rate of childhood wasting to less than 5%

Table 2. Number of countries on- and off-course to achieve WHA Global Nutrition Targets for 2025[7]

WHA nutrition indicator*	On-course in 2016	Off-course in 2016	
		Little/no progress	Some progress
Child stunting	41	15	58
Child wasting	134	63	-
Child overweight	53	24	22

WHA, World Health Assembly
*For children under the age of 5 years
Adapted from: International Food Policy Research Institute. Global Nutrition Report 2016: From promise to impact: ending manutrition in 2030. Washington, DC. Available at: http://ebrary.ifpri.org/utils/getfile/collection/p15738coll2/id/130354/filename/130565.pdf

End Childhood Obesity (ECHO) initiative of the WHO aims to prevent and treat childhood and intergenerational cycle of obesity on a global scale through multifaceted interventions especially aimed at early life when growth is most amenable to change.[12]

General implications of early life nutrition

Maternal malnutrition (including both under- and over-nutrition) can have profound consequences for embryonic development and fetal growth, and for subsequent infant growth and development during and beyond the breastfeeding period. As discussed in subsequent chapters, under- and over-nutrition during gestation places a fetus at increased risk of pregnancy complications and adverse birth outcomes,[14,15] and increases the odds of subsequent infant morbidity and mortality,[1] and longer-term adverse outcomes.[16]

Adequate nutrition continues to be important throughout infancy, childhood, and adolescence. Adequate nutrition tailored to each specific stage of development during the first two years after birth supports children in achieving an appropriate growth trajectory,[7] and can help prevent adverse health effects in later life[4,6] (**Table 3**).

Table 3. General risks associated with malnutrition during gestation, infancy, and early childhood

Under-nutrition
• Greater infectious disease burden (e.g. diarrhea, respiratory diseases, tuberculosis, malaria)[1,7]
• Increased risk of infant/child mortality[1]
• Impaired cognitive development (potentially irreversible)[6]
• Nutrition-related chronic cardio-metabolic diseases in later life (especially when accompanied by rapid or excessive catch-up weight gain in later childhood)[17–20]
Over-nutrition
• Excessive adipose tissue deposition associated with rapid (or catch-up) growth (may be irreversible)[21–23]
• Childhood morbidity (e.g. asthma, musculoskeletal impairment, early-onset cardiometabolic disturbances)[10,12]
• Adult obesity and its cardiometabolic consequences, e.g. diabetes[12,24]

Growth monitoring and growth standards

During pregnancy fetal growth is monitored, most often after the first trimester when pregnancy is confirmed and women present themselves for regular checkups. Healthcare professionals have the opportunity to discuss the importance of nutrition to support normal fetal growth with the mothers. Increasingly, ultrasound is used to monitor crown-rump length, head size and femur length, for example, as appropriate measures to track fetal growth. Serial fetal growth measurements may be compared with an established growth standard such as the INTERGROWTH-21st fetal growth standards (see **Chapter 2** and **Appendix**).[25,26]

Growth monitoring (e.g. weight, length, and head circumference) should continue after birth. Weight and length/height assessments should be performed regularly throughout early childhood. Standard anthropometric measures are evaluated using standardized, sex-specific

growth charts to assess weight-for-age, height-for-age, weight-for-length, and body mass index (BMI) patterns (see **Table 4**). As described in **Chapter 3**, it is known that when infants, raised in optimal living conditions by healthy, non-smoking mothers, are breastfed according to WHO recommendations (i.e. exclusive or predominant breastfeeding for 6 months, introduction of complementary foods around 6 months, and continued partial breastfeeding for at least up to 12 months, but more preferably up to 24 months[6,27]), they tend to show a predictable pattern of growth up to the age of 5 years, regardless of genetic differences.[5,6,27,28] This demonstrates the relevance of appropriate nutrition and feeding throughout infancy to ensure optimal growth.

At the front line: The role of healthcare professionals

Irrespective of geographical location or socioeconomic situation, maternal health before and during pregnancy is crucial to secure the best start for an infant at birth. Pregnancy is a unique period during which women are often highly motivated to make positive behavioral changes,[29] and healthcare professionals play a pivotal role in working with women planning to conceive, and with expectant and lactating mothers. This is a unique opportunity to set the stage to promote maternal and infant health and wellbeing, particularly through encouraging healthy lifestyle choices to ensure adequate and proper nutrition during the first 1,000 days. In particular, mothers should be advised to breastfeed exclusively for the first 6 months according to WHO recommendations.[30]

Through increased attention to maternal and infant nutrition status and healthy eating habits, with a focus on education, evaluation, monitoring, and intervention, healthcare professionals can positively impact health at the individual, family, and ultimately the population level (**Figure 1**). Through identification of at-risk populations and implementation of strategies to prevent malnutrition, healthcare

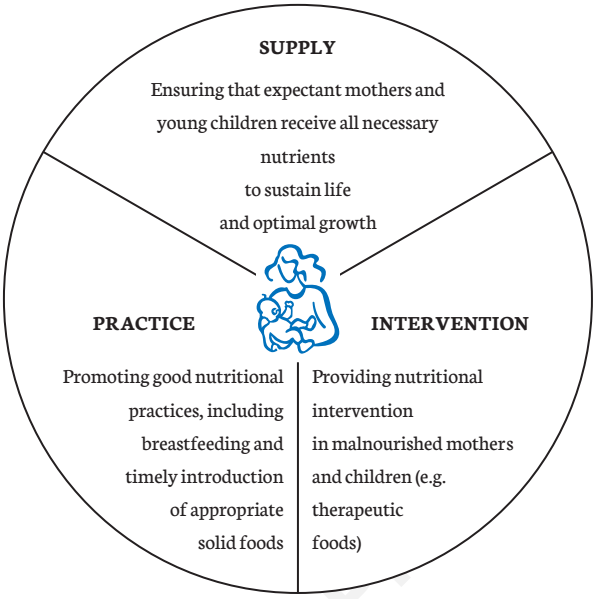

Figure 1. Ensuring adequate nutritional status during the first 1,000 days: the role of the healthcare professional[1]

professionals in respective countries are key drivers enabling the achievement of the global WHO targets.

Purpose of this Essential Knowledge Briefing

In light of the immense worldwide double burden of malnutrition and the important role of healthcare professionals in the global efforts to combat it, this book provides a comprehensive overview of the most recent research to provide recommendations and insights into maternal, infant, and child nutrition, and possible implications for fetal, infant, and child growth and development during the first 1,000 days.

Optimal patterns of fetal, infant, and early childhood growth are highlighted, along with recommended growth standards for each stage (**Table 4**). We discuss compromised fetal growth as well as post-

natal growth deviations as indicators of malnutrition, with their risks and prognoses. In addition, the specific nutritional challenges associated with preterm birth are highlighted and possible intervention opportunities during the first 1,000 day window tailored to specific needs are presented to reduce the risk of adverse outcomes in infancy and beyond.

Table 4. Recommended international growth monitoring tools

Population	Recommended/suggested standards
Fetuses*	INTERGROWTH-21st standards for fetal growth[26]
Infants at birth*	INTERGROWTH-21st standards for birth weight[31]
Preterm infants*	Fenton charts[32,33] Olsen charts[34]
Infants-toddlers-children (0-5 years)	WHO Child Growth Standards[27] (available for download at: http://www.who.int/childgrowth/standards/technical_report/en/index.html)

*Refer to Appendix for charts

Chapter highlights

- Adequate nutrition during the first 1,000 days, including good maternal nutritional status before and during pregnancy, and appropriate nutrition during infancy and toddlerhood, is a fundamental prerequisite for individual survival, optimal growth and development, and lifelong health.
- The "double burden" of malnutrition (under- and over-nutrition) is a global problem, encompassing growth failure, stunting, and micronutrient deficiency on one hand, versus overweight and obesity on the other.
- Under- and over-nutrition during first 1,000 days are risk factors for various adverse outcomes, including impaired growth, failure to thrive, infant/childhood morbidity and mortality, and the development of non-communicable diseases in adulthood, such as cardiovascular disease and diabetes.
- When infants born to well-nourished, healthy mothers, and living in an environment free of socio-economic constraint are exclusively breastfed for about 6 months, with continued breastfeeding until 1 year of age and introduction of adequate complementary feeding around 6 months, tend to show a predictable pattern of growth and body composition development. Adverse environmental factors, particularly poor nutritional status, may influence normal patterns of linear growth and weight gain.
- In 2012, the World Health Assembly established six key global nutrition targets for the year 2025, which were endorsed by the WHO member states. Although global progress is currently off-track to achieve these targets in many countries, particularly a reduction in childhood overweight and obesity, progress continues to be monitored.
- Healthcare professionals play a pivotal role in promoting optimal growth, development, and wellbeing during prenatal and postnatal life, partially through helping to ensure adequate and proper nutrition for both mother and child during the first 1,000 days.

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SECTION A

Healthy growth

Chapter 2

Fetal growth

The fetal growth continuum

Gestation is a remarkable journey of growth and development spanning up to 37-42 weeks. The embryo begins to implant in the uterus approximately six days after conception, and the formation of the placenta starts.[1] Both the embryo and placenta undergo a period of rapid change through cell multiplication and differentiation, establishing the basis for the formation of body tissues and organs in the embryo, and the formation of the maternal-fetal interface of the placenta.[1,2] During this initial stage, embryonic growth is solely dependent upon maternal health and nutrition status, as the placenta is not yet functional, and there is no exchange between the fetus and the external environment.[1]

Around the 10th week of pregnancy (8 weeks since conception), an embryo enters the fetal stage of development.[1,2] The placenta starts to become functional, interacting with the endometrium and orchestrating various maternal adaptations to the pregnancy,[1] and also enabling the fetus to be supplied with nourishment through the maternal arterial circulation.[1,2] After the first trimester, both the placenta and the fetal organs continue to grow and develop, but fetal growth is most rapid between 22 and 40 weeks, when a six-fold increase in fetal weight is observed.[3] During this period, the fetal body organs are not only increasing in size but also in functional complexity, in preparation for later interaction with the external environment.

At around 25 weeks' gestation, adipose tissue development begins, and the fetus continues to increase its fat stores until full term.[2] Of all mammalian species, the body fat percentage at birth is relatively high in humans. Linear growth (but not weight gain) slows slightly over the last part of the third trimester,[4] a phenomenon known as maternal restraint.[5]

Although birth weight can be considered an indicator of intrauterine conditions,[6] this is a crude measure that may not adequately describe individual variability in fetal growth patterns or body composition.[7-10]

Fetal brain and lung development

The development of the brain starts soon after conception, and continues with rapid growth throughout gestation (see **Figure 2**).[11] At birth, an infant brain weighs one quarter that of an adult brain, even though the neonate's body weighs less than one tenth of an adult's body.

- At around 5 weeks' gestation: the neural plate at the back side of the embryo is formed.
- Between 7 and 22 weeks' gestation: a total of around 20 billion neurons are produced through neurogenesis, and migrate to their ultimate locations in the brain.
- Between 20 and 35 weeks' gestation: neural cells become organized, and the cortex is established, which plays a key role in cognitive and behavioral function.
- At around 24 weeks' gestation: nerve fibers and synapse formation ("wiring") begins, and individual adjustment of the neural network starts by elimination ("pruning") of more than 50% of the neurons and circuits. This pruning occurs in three consecutive waves (once during fetal life, once during early childhood, starting around 3 years of age, and once starting just before adolescence).
- During the last few weeks of gestation, the myelination process starts, which is essential for proper development, fine-tuning, and maintenance of brain function.[11]

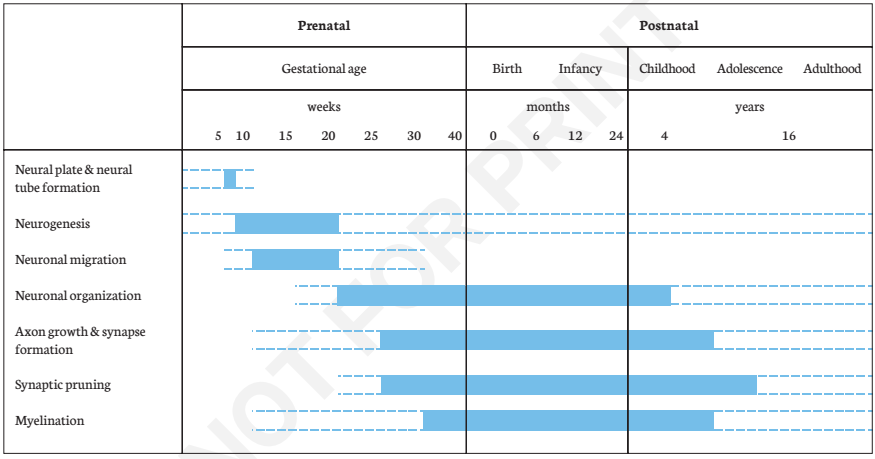

Figure 2. Timetable of major events in human brain development during prenatal and postnatal life. Blue-shaded areas indicate peak activities, open lined areas indicate low or medium activity.

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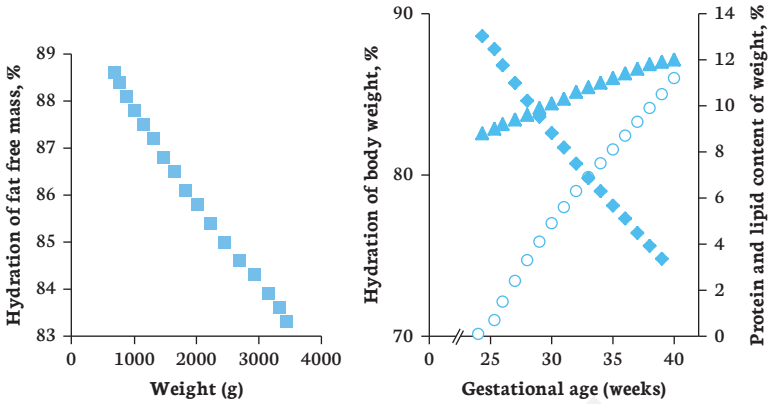
In parallel with the development of the brain and other organs, prenatal development of the lungs represents another crucial aspect of fetal growth, despite the fact that the lungs as breathing organs are unnecessary for intrauterine existence. Nevertheless, they must be developed *in utero* to such an extent that they are immediately ready to function following birth.[12] Lung development extends from the embryonic period through the fetal period up to birth, and even beyond, meaning that infants born prematurely experience specific challenges related to their functionally immature lungs at birth (see **Chapter 4**).[13]

Fetal body composition

Fetal body composition changes throughout the pregnancy continuum (**Figure 3**). The fetus has a minimal percentage of fat until 24 weeks' gestation, after which fat deposition increases dramatically; a normal full-term neonate has approximately 17% body fat. The percentage of body fat at birth may be dramatically higher in the case of maternal obesity, excess maternal gestational weight gain, or maternal pregnancy complications such as gestational diabetes.[14,15] In particular, maternal obesity is associated with increased fetal abdominal fat accumulation.[15]

Gender differences in body fat also exist; at birth, female infants tend to have slightly higher adiposity compared with male infants.[14] In addition, infants born after intrauterine growth restriction tend to have lower total adiposity.[16]

Body protein content is low during the first 20 weeks of pregnancy, and accelerates thereafter,[14] as the fetus shows increased development of muscle tissue and other organs.[2] Hydration levels are reported to be approximately 90% early in fetal life, and remain above 80% at full term, but decrease after birth, which explains the typical transient weight loss observed in the first 2-3 days after birth.[14] Fetal bone



*Ziegler:[28] Body composition of the reference fetus, ■, Hydration of fat-free mass (%, g/100 g FFM); ◆, Hydration of body weight (%, g/100 g of body weight); ▲, Protein content of body weight (%, g/100 g of body weight); ○, Lipid (%, g/100 g of body weight).

Figure 3. Fetal body composition changes during gestation[14,18]

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mineral accretion is greatest during the second half of gestation, with the rate reaching maximal levels during the third trimester of pregnancy.[17]

Factors influencing fetal growth

Fetal growth is determined by a range of maternal, placental, and fetal factors.

Although the genetic makeup is complete at conception and initiates growth and organ development, a range of environmental factors (discussed below) can alter the course of growth and development.[19] Maternal nutrition and oxygen supply via the placenta are pivotal drivers of fetal growth,[4,19] but the fetal hormonal environment – mostly steered by hormones produced and secreted by the placenta, and also by the fetus itself – mediates growth by controlling the distribution of nutrients with regard to oxidative metabolism and tissue growth and differentiation.[19] Consequently, optimal placental

size and functional development are crucial to meet fetal nutrient needs and ensure a normal hormonal milieu. Early placentation (i.e. how the placenta is attached to the uterine wall) also plays a major role in the function of the placenta,[1] and deviations in growth, function and final size of the placenta are mostly responsible for growth restriction as well as excessive growth.[20]

Epidemiological studies help to increase our understanding of the associations between various nutritional, socioeconomic, and other environmental exposures and different anthropometric outcomes (e.g. birth weight, lean mass, and adiposity). Evaluation of different measures of body size and composition is important to establish the full picture of overall fetal growth; infants may be genetically large but not have a high proportion of body fat, and vice versa.[14,21]

In compromised pregnancies (e.g. cases of under- or over-nourishment, gestational diabetes, or preeclampsia), changes in the intrauterine growth of specific tissues and organs can have irreversible functional consequences[19] (discussed below). A greater understanding of specific adverse nutritional and other environmental factors will help in formulating future intervention strategies to improve birth outcomes and long-term health.[21]

Pre-conception

1. Parental characteristics

The mechanisms by which pre-pregnancy parental factors determine infant anthropometric outcomes at birth are not fully understood,[21] but several factors are thought to influence subsequent fetal growth (**Figure 4**).

Maternal and paternal heights are positively associated with neonatal birth weight and skeletal size.[22,25] In two large studies, short maternal stature was shown to be a risk factor for low birth weight and

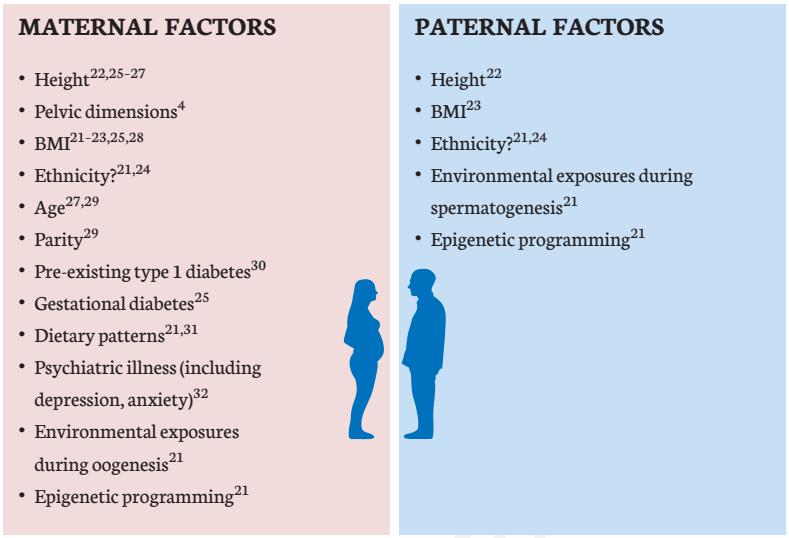

Figure 4. Pre-conception factors influencing fetal growth

stunting.[26,27] Smaller maternal pelvic dimensions can also limit the ability of a fetus to grow.[4] However, it should be noted that, if an infant is genetically predisposed to small stature and there is no evidence of compromised nutritional status, there is probably no cause for medical concern.

High pre-pregnancy maternal BMI shows a strong positive association with both neonatal adiposity (increased body fat at birth) and large-for-gestational-age (LGA) births.[21-23,25,28] This probably reflects conditions in the intrauterine environment,[21] and thus highlights the importance of maternal physiology and body composition.[22] However, not all infants born to obese mothers are LGA, confirming the involvement of various environmental and genetic factors in the regulation of placental nutrient transfer.[21] Interestingly, a weak positive association has been demonstrated between paternal BMI and neonatal BMI.[23] In addition, it has been suggested that

environmental exposures during egg/sperm production may affect fetal growth and development.[21]

Nulliparous status (compared with multiparous status) and young maternal age – which may result in maternal restraint – have been associated with higher incidence of small-for-gestational-age (SGA) births[27,29,33] (see **Chapter 5**). The reasons for this are unclear, but it is plausible that young mothers may not yet have completed their physical growth and maturation, and that a pregnancy may therefore impose a relatively large nutritional burden.[29] A short inter-pregnancy interval is also associated with fetal growth restriction.[33]

There is some evidence to suggest that women with prenatal psychiatric conditions such as depression, anxiety, and obsessive compulsive disorder are at increased risk of poor fetal growth during pregnancy.[32]

While some differences in fetal growth and neonatal body composition have been reported among different ethnic groups,[24,34] a large international study in healthy pregnant women in optimal conditions has shown remarkable consistency in fetal growth between different populations, suggesting that apparent ethnic differences are more likely to be attributable to maternal health and nutrition status than to ethnic differences in growth potential.[35,36]

2. Maternal pre-conception dietary patterns

Adequate and appropriate nutrition before pregnancy is related to favorable perinatal outcomes, whereas pre-conception dietary patterns consisting of high-fat, high-sugar foods, and frequent consumption of takeout foods have been associated with shorter neonatal body length.[31] Some studies have also suggested a link between pre-pregnancy maternal diet and early placental development affecting later placental growth and function, but the precise mechanisms are unclear.[21] Thus, improvement of dietary habits before conception appears to be an important priority for subsequently optimal fetal growth.

A nutrition working group of the International Federation of Gynaecology and Obstetrics (FIGO) has recently published a comprehensive report emphasizing current consensus and recommendations on female adolescent, preconception, and subsequent maternal nutrition.[37] This document provides an elaborate and complete overview of the importance of balanced nutrition in general, the crucial role of specific nutrients for specific stages of development, and the risks of nutrient deficiencies, in light of the trans-generational effects of such deficiencies.[37]

During pregnancy

A multitude of different factors during gestation may positively or negatively influence fetal growth and weight gain. It has been demonstrated that an unfavorable intrauterine environment could affect fetal growth as early as the tenth week of pregnancy,[8] at which time the embryo transitions to fetal life.[2] However, many of the suspected factors are inter-related, and causation is difficult to definitively establish as a basis for recommendations. This is particularly the case when studying the influence of maternal nutritional factors on fetal growth, as multiple confounders are difficult to rule out.

Key factors that are thought to influence fetal growth are listed in **Figure 5**, and described in more detail below and in **Chapters 5** and **6**.

1. Fetal characteristics

Male gender is associated with higher birth weight,[7,38] although the difference in birth weight between males and females has decreased over time.[38] Body composition is also different between male and female neonates, with female neonates showing lower fat-free mass and higher adiposity compared with males.[7,39]

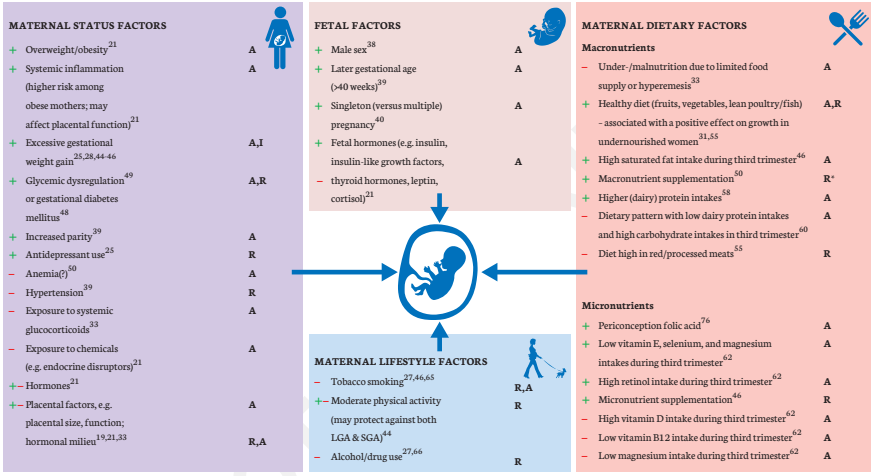

Figure 5. Factors during gestation that may influence human fetal growth and/or birth weight

"+" represents factors thought to drive faster fetal weight gain; "-" represents factors thought to be associated with slower fetal weight gain and/or lower adiposity.

Evidence: R = review articles; A = associative (observational) studies; I = intervention studies. Note that most references cited in Figure 5 are reporting or reviewing observational data showing associations between different factors and fetal growth. Very limited interventional data are available to date. In associative/observational studies, the reported associations have been suggested in multiple studies, but the strength of the evidence ranges from low to intermediate. The references included in the figure provide examples of reported associations.

BMI = body mass index; LGA = large for gestational age; SGA = small for gestational age.

*Low-income countries only

Higher gestational age[39] and singleton pregnancy (versus multiple)[40] are positively associated with birth weight. Caucasian ethnicity (compared with Asian/Other) may also be positively associated with birth weight,[39] and body composition also varies between some populations. For example, despite a lower average birth weight in Indian infants, there is some evidence of greater adiposity in the Indian population.[41–43]

2. Maternal characteristics

Along with pre-pregnancy overweight and obesity, excessive gestational weight gain is becoming increasingly common,[44] and has been strongly associated with higher infant birth weights;[25,28,44–46] although not all studies have confirmed these observations.[39]

Excessive weight gain during pregnancy is a risk factor for maternal glycemic dysregulation/gestational diabetes,[44,47,48] which, in turn, is associated with neonatal central adiposity,[49] a higher likelihood of LGA birth,[25] and macrosomia (high absolute birth weight).[30] Appropriate gestational weight gain is discussed in **Chapter 6**.

Maternal anemia during pregnancy has been shown to be associated with lower birth weight in some populations, but not in others.[50] Maternal hypertension may also predispose toward a lower fetal body fat percentage.[39]

3. Maternal nutrition and placental function

Optimal nutritional supply to the developing fetus is critical in achieving appropriate growth and development.[51] Over the course of a pregnancy, maternal energy and nutrient requirements increase slightly to support the increase in metabolism, tissue expansion, blood volume and red cell mass expansion, and nutrient delivery to the fetus.[51] Current evidence suggests that both macronutrient and micronutrient intakes are far from optimal in many countries.[51] This may be a logical consequence of insufficient adaptation of the diet to meet pregnancy demands; the relatively small increase in total energy

demands may pose a challenge with regard to satisfying specific increased micronutrient and protein requirements resulting from pregnancy.[37]

This is of great concern, because it is well established that inadequate maternal nutrition during pregnancy can affect fetal development and have substantial effects on newborn morbidity.[33] Even if nutrient deficits are relatively small, if present for the entire duration of pregnancy they may have a significant impact. The Dutch Famine studies have demonstrated that the *timing* of specific nutritional deficits or insults during pregnancy is critical in determining which organ systems are most affected.[52]

Because after the first trimester, nutrients delivered to the fetus via the placenta drive fetal growth,[19] the placenta is a key player in mediating birth outcomes.[1,21,33] Placental size and function develop progressively throughout gestation, and optimal placental development early in pregnancy is crucial for adequate nutrient transfer capacity during the final trimester, when, in absolute terms, fetal growth is greatest.[1,21]

> The placenta is a key player in mediating birth outcomes. Optimal placenta development early in pregnancy is crucial for adequate nutrient transfer during the final trimester when fetal growth is greatest.

Rather than being a passive channel for nutrient transfer between mother and fetus, the placenta actively and efficiently responds to both maternal and fetal signals to regulate placental transport and metabolic function.[1,21,33] In response to varying nutrient and oxygen availability via the placenta, fetal hormones such as insulin, insulin-like growth factors, thyroid hormones, leptin, and cortisol act

to optimize the growth of the fetus within genetically pre-programmed parameters, by regulating cellular nutrient uptake at the maternal-fetal interface.[19,21,53]

Pregnant women may be undernourished for several reasons, including limited food supply, inadequate food and nutrient quality of the diet, or severe nausea and vomiting persisting beyond the first trimester.[33] During the course of the pregnancy, lasting maternal under-nutrition can result not only in fetal undergrowth, but also in a compensatory overgrowth of the placenta, depending upon the specific type and severity of nutrient deprivation and the trimester during which the deprivation occurred.[33] Maternal under-nutrition can also inhibit proper development of the nutrient transfer interface of the placenta, leading to persistent effects on fetal nutrient supply.[21,33] Furthermore, it is thought that nutritional deprivations and other environmental factors (e.g. exposure to stress hormones) during early pregnancy may alter the expression of genes involved in placental nutrient transfer at later gestational stages.[21,33,54]

> Nutrition deprivations and other environmental factors during early pregnancy may alter gene expression involved in placental nutrient transfer at later gestational stages

4. Maternal dietary and lifestyle factors

A number of specific maternal dietary and lifestyle factors appear to influence fetal growth,[46] although the evidence is fragmented.[51]

Maternal macronutrient intake appears to directly affect birth weight. The literature suggests that a high consumption of whole foods, including fruits, vegetables, low-fat dairy products, and lean meats (particularly poultry and fish), throughout gestation is

associated with healthy neonatal birth weights and decreases the risk of giving birth to an SGA infant.[51,55] In contrast, a maternal diet characterized by a high consumption of red and processed meats and high-fat dairy products increases the risk of giving birth to an SGA infant, irrespective of parental anthropometric characteristics or maternal smoking status.[55] Note that animal experimental evidence clearly suggests that there is a u-shaped association between maternal protein intakes and intrauterine growth; both protein under-nutrition and protein over-nutrition are associated with fetal growth restriction.[56,57]

A high consumption of whole foods, including fruits, vegetables, low-fat dairy products, and lean meats (particularly poultry and fish), throughout gestation is associated with healthy neonatal birth weights and decreases the risk of giving birth to an SGA infant.

Higher maternal dairy product intake, regardless of dairy fat content, has been shown to have growth-promoting effects on the fetus in some studies,[58,59] but not others.[59] However, taken together, prospective evidence suggests that moderate dairy product consumption, relative to no or low dairy intake (or extremely high animal protein intakes), may positively influence fetal growth in healthy Western populations.[59]

One study has specifically shown that a high intake of refined carbohydrates during early pregnancy may suppress placental and fetal growth, especially when combined with a low intake of high-quality protein (i.e. dairy protein) in late pregnancy.[60] A diet high in saturated fat during the third trimester has been associated with increased neonatal adiposity.[46]

Little is known about the effect of maternal micronutrient intake in relation to fetal growth. There is some evidence that maternal micronutrient supplementation has a positive influence on birth weight, but not birth length.[61] A large recent study also suggested that high vitamin D intake and low vitamin B12 intake during the third trimester may be associated with low birth weight, and that low magnesium intake during the third trimester predicts shorter body length at birth. High retinol intake and low vitamin E, selenium, and magnesium intakes during the third trimester were associated with anthropometric measurements that reflect a greater degree of adiposity at birth.[62] It should be noted that most of the evidence regarding the effects of maternal micronutrient intake on fetal growth is derived from epidemiological studies, and not from randomized trials.

With regard to intake of supplements during pregnancy, a large meta-analysis of at-risk pregnant women in Africa showed improved birth weight outcomes and infant mortality risks after both micronutrient and macronutrient supplementation.[50] It is likely that also the diet of these women prior to (as well as during) pregnancy was inadequate.

5. Exercise

Increased physical activity during pregnancy, when not contraindicated, may help prevent maternal glycemic dysregulation and improve overall wellbeing.[44] Although the current evidence does not indicate a direct effect of exercise on birth weight,[44,63] moderate physical activity appears to be safe, and may help to protect against both birth weight extremes (SGA and LGA).[44] One study also suggested that exercise training may help reduce the adverse effects of maternal obesity on infant birth size.[64] It is thought that regular physical activity may also improve blood flow and functional capacity of the placenta, thus improving nutrient delivery.[44]

6. Chemical, substance, and pharmaceutical exposures

Fetal exposure to parental (particularly maternal) tobacco smoking is known to be very strongly associated with fetal growth restriction, preterm birth, and low birth weight,[46,65] with one study even showing a dose-dependent correlation.[65] Alcohol consumption during pregnancy has also been associated with decreased birth size in multiple studies, including epidemiological studies.[66,67]

Some drugs, including illicit drugs, may also adversely affect fetal growth and development.[27,66] These effects may be direct or indirect; indirect effects may include compromised delivery of nutritional components because of placental insufficiency, or poor maternal nutrition choices secondary to drug abuse.[66]

Furthermore, animal studies have suggested that exposure of a pregnant mother to some environmental chemicals (e.g. endocrine disruptors such as bisphenol-A) might adversely affect fetal growth.[21,68]

Key fetal growth milestones and monitoring measures

Birth weights have increased in many first-world countries over the past quarter of a century; although initially related to an improved overall health and nutrition status, current trends are more likely due to a combination of increasing pre-pregnancy maternal BMI and gestational weight gain as well as pregnancy complications such as gestational diabetes.[69,70] However, given the concurrently high global prevalence of SGA births, screening for both fetal overgrowth and undergrowth remains a major global public health priority.[35,36]

Fetal growth standards are important tools that enable healthcare professionals to monitor growth against national or international benchmarks, such as the INTERGROWTH-21st fetal growth

standards, discussed in the next section. Globally, diagnoses of fetal growth restriction are often made at different levels of care, even within the same geographical regions.

Moreover, over one hundred different growth charts with different cutoff points are available.[35,36] In addition, preterm growth charts such as the well-established Fenton charts[3,71] (discussed in **Chapter 4**) exist, but these are specific for extrauterine, rather than intrauterine growth.[3] Fetuses remaining *in utero* may grow at different rates and with different anthropometric outcomes compared with infants born early who have necessarily adapted to a completely different form (and route) of nutrition.[72]

Such inconsistencies complicate the clinical assessment of fetal nutritional status, and may lead to missed opportunities for early detection and intervention of growth deviations, or may even lead to inappropriate interventions.[35,36] The absence of an international fetal growth standard until recently has thus been a major limitation.[36]

INTERGROWTH-21st Project fetal growth standards

A new set of sex-specific international standards for fetal growth were published in 2014 to complement the available WHO standards for

INTERGROWTH-21st growth charts

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postnatal growth.[35,36] The WHO standards will be discussed in detail in **Chapter 3**. These fetal growth standards were based on a multicenter, population-based study – the Fetal Growth Longitudinal Study (FGLS) – which formed part of the INTERGROWTH-21st Project. Participants were exclusively healthy, well-nourished women with singleton pregnancies, at low risk of adverse outcomes or fetal growth restriction, from eight geographically diverse populations. Assessment of fetal growth was based on serial ultrasound measurements of head circumference, biparietal diameter, occipitofrontal diameter, abdominal circumference, and femur length, taken every five weeks between 14 and 42 weeks' gestation.[35]

Robust analysis techniques demonstrated good consistency in fetal growth between the eight cohorts, indicating that the INTERGROWTH charts describe "optimal" intrauterine growth and are a sound reference standard for fetal growth in diverse populations.[35,36] This consistency between ethnic groups suggests that deviations in fetal growth are more likely to be attributable to environmental factors such as maternal malnutrition, rather than genetic factors.

Because the INTERGROWTH fetal growth standards and the WHO infant/child growth standards have similar methodologies, these two standards may be used in tandem for seamless monitoring of growth from early pregnancy through early childhood.[36] The birth weight standard is represented in **Figure 6** as an example; see the **Appendix** for other INTERGROWTH-21st standards.

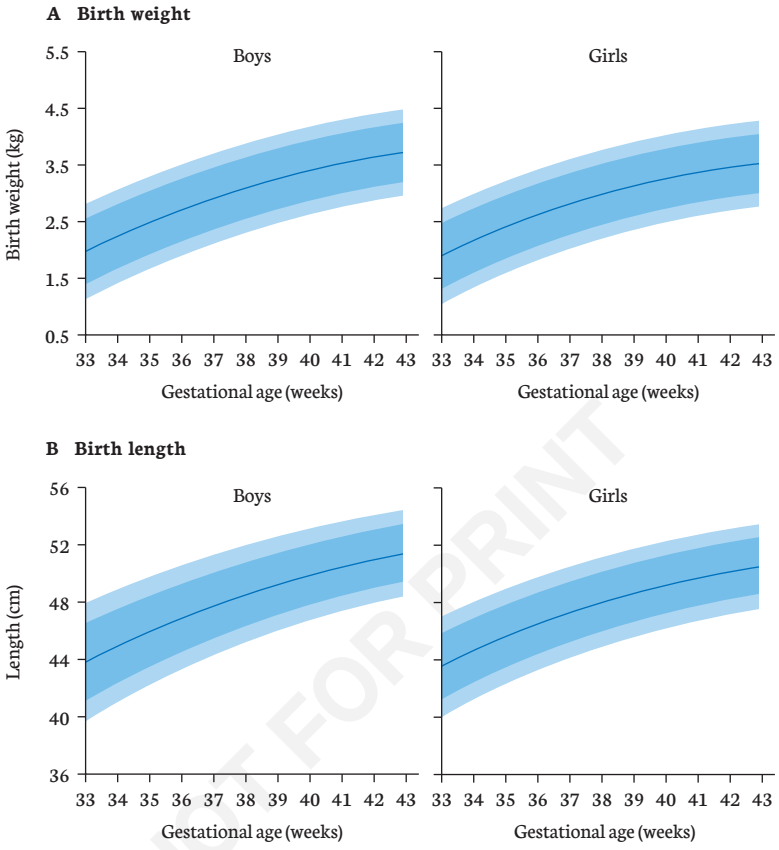

Figure 6. International fetal growth standard for birth length and weight according to gestational age and sex (INTERGROWTH-21st Project) [36]

3rd, 10th, 50th, 90th, and 97th smoothed centile curves for birth weight. Additional charts for head circumference according to gestational age are found in the Appendix. Data were limited to infants born at or after 33 weeks' gestation.

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Fetal programming and its short- and long-term consequences

Compromised or excessive fetal growth may have both short- and long-term adverse consequences, through fetal programming or the Developmental Origins of Health And Disease (DOHaD) principle.[33,50,51,73,74] Fetal programming refers to adaptations in structure or function that may occur in the fetus in response to maternal over- or under-nutrition or other environmental insults. These effects may be mediated by adaptations in gene expression, resulting in durable differences in organ development and gene function.[4,33] Such alterations may occur even in the absence of changes in birth weight.[1]

> Compromised or excessive fetal growth may have both short- and long-term adverse consequences, through fetal programming . . . Fetal adaptations in response to nutritional stress and other environmental insults, while advantageous for short-term survival, can have important implications for postnatal development and disease susceptibility in later life.

For example, it has been postulated that developing fetal organ systems (e.g. pancreas, liver, or blood vessels), when undergoing critical periods of functional development, may make necessary adaptations such as slowing the rate of cell division or cell/organ maturation, in response to reduced or excessive nutrient availability. This can result in altered tissue function and 'resetting' of metabolic systems. It is thought that even brief periods of under- or over-nutrition may permanently alter tissue cell numbers and physiologic and metabolic processes.[4,74] These adaptations, while advantageous for short-term survival, can have important implications for postnatal development and disease susceptibility in later life.[4,33,50,75]

Intrauterine stress – either physiological (e.g. nutritional insults, obstetric complications, or infection) or psychosocial (e.g. social/economic disadvantage or a major life event) – is thought to be another important aspect of fetal programming.[73] It has been suggested that stress exposure during gestation may contribute directly to changes in metabolic endocrine, cardiovascular, and behavioral phenotypes in the infant, and also may augment the adverse effects of any maternal under- and over-nutrition. These effects are mostly likely mediated by stress-related hormonal and immune/inflammatory mechanisms in both the mother and fetus.[73]

Both animal models and human studies support the principle of fetal programming. Each have their limitations; however, the overall body of evidence is becoming increasingly strong.[74] Adverse short- and long-term consequences of fetal programming are discussed in more detail in **Chapters 5** and **6**.

Chapter highlights

- While genetic makeup is already complete at conception, a range of different environmental factors can alter the predetermined course of fetal growth and development.
- Maternal nutrition and oxygen supply are the pivotal drivers of fetal growth, with other socioeconomic and demographic variables also influencing fetal growth rates.
- Pre-conception factors that appear to influence fetal growth include parental genetic characteristics, maternal BMI and age, parity, interpregnancy interval, maternal diabetes, and maternal dietary patterns.
- Many post-conception factors have also been implicated in fetal growth outcomes. These include:
  - Fetal factors (e.g. gender, singleton vs. multiple pregnancy, fetal hormones)
  - Maternal factors (e.g. excessive gestational weight gain, hypertension, chemical/pharmaceutical exposures, hormonal and placental factors)
  - Maternal dietary factors (e.g. input of various macronutrients and micronutrients)
  - Lifestyle factors (e.g. smoking, physical activity, and alcohol/drug use)
- Maternal malnutrition (including both under- and over-nutrition) and intrauterine stress may lead to either compromised or excessive fetal growth, both of which may have both short- and long-term adverse consequences through a phenomenon known as "fetal programming". The timing of nutritional insults during pregnancy determines which organ systems are affected; fetal adaptations may involve irreversible changes in the growth of specific fetal tissues and organs to ensure short-term survival.

- While advantageous in the short term, such adaptations can have important adverse implications for postnatal development and susceptibility to non-communicable diseases in later life.
- Given the global prevalence of both SGA and LGA births, screening for both fetal undergrowth and overgrowth remains a major public health priority.
- A variety of anthropometric measurements are used to evaluate fetal growth, including ultrasonographic measurements and postnatal measures of weight, length, BMI, lean mass, and adiposity. A new set of international standards for fetal growth were published in 2014 as part of the INTERGROWTH-21st Project, to complement the available WHO standards for postnatal growth.

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Chapter 3

Postnatal growth

From birth to the age of 2 years, a child's weight increases four-fold. At 2 years, a child has reached approximately 50% of their expected adult height, and approximately 90% of their expected adult head circumference.

Over the past few decades, substantial evidence has been generated to show that early growth rates can have lasting effects on health in childhood and later life.[1,2] Children raised in a healthy environment, born to a healthy mother, and raised free of malnutrition in the post-natal period, are more likely to achieve their full genetic potential with regard to growth and development, enabling them to substantially contribute to family, community, and country, and help drive sustainable development.[3]

Measuring and monitoring growth is an important and efficient tool to define child health and nutritional status, both on an individual level as well as at the population level, and is therefore an essential aspect of infant and child healthcare.[4–6] Defining the 'optimal' growth pattern is, however, challenging, as infants are a heterogeneous population undergoing rapid changes in body composition,[7,8] and definitions and ranges of growth parameters vary widely.[9] The international WHO growth standards (described in detail in the next section) and various national growth reference curves represent common growth patterns, but the cutoff points used are based on crude statistical methods, rather than on clinical evidence of short- or long-term adverse effects of growth deviations.[10]

Adequate growth monitoring in infancy and early childhood is, however, essential to ensure timely diagnosis of growth deviations and appropriate intervention when necessary. Of particular interest are the clear association between rapid weight gain in infancy and later development of obesity and cardiometabolic disorders[9,11–13] (see **Chapters 4-6**), and the association between stunting and a persistent

reduction in height and cognitive capacity throughout childhood[14,15] (see **Chapter 7**). Hence, when considering ideal rates of weight gain and linear growth, an appropriate balance between short- and long-term health benefits should be respected.[8]

This chapter focuses on anthropometric measurements of growth; but it is clearly important to consider all aspects of child development, including also cognitive, motor, and socio-emotional development, when evaluating a child's health and development.[14,16]

Growth during infancy

Directly after birth, most infants have an initial weight loss of 3-6% in the first 2-3 days after birth, the majority of which is explained by water loss. This early weight loss is usually regained within 10 days postpartum.[17,18] In the first 3-4 months thereafter, growth velocity is very high, with a peak weight gain velocity of about 30-35 g/day between 1-2 months of age.[11,16,19] After this, weight gain velocity falls rapidly, achieving a more linear pattern of growth at a slower pace, and remains stable at approximately 5-6 grams per day up to 5 years of age (please refer to the WHO Child Growth Standards, available at: http://www.who.int/childgrowth/standards/technical_report/en/index.html).[16] These changes in weight gain velocity are paralleled by a similar, but less pronounced pattern of length gain during infancy, resulting in a doubling of length within the first four years.[16,19,20]

These rapid changes in weight and length gain result in a typical pattern of BMI development throughout infancy and childhood. BMI peaks around 6-9 months of age,[13,16,21] and after 12 months of age, relatively more investment is in length.[16] Consequently, BMI declines over the next few years as adiposity remains stable while linear growth continues, and BMI reaches its lowest levels around 5-7 years of age. This is termed the "adiposity rebound", because it is followed by a second period of rapid growth in body fat (**Figure 7**). BMI increases

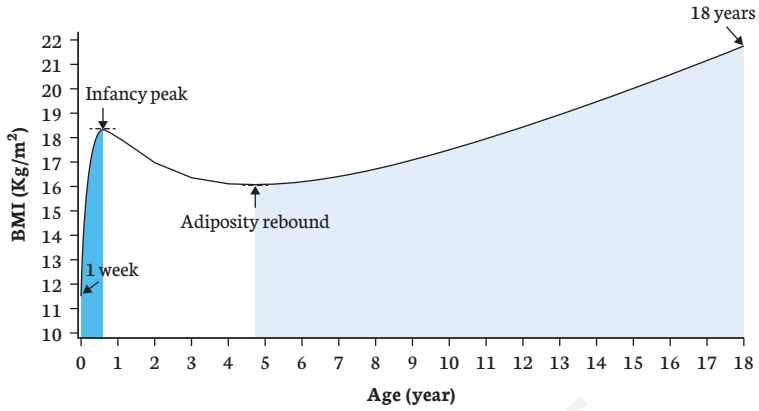


Figure 7. Typical BMI trajectory of healthy growth throughout childhood[21]

Adapted with permission from: Wen, et al. *BMC Med Res Methodol* 2012;12:38.

further at the onset of puberty, reaching adult BMI levels around 18 years of age.[21,22]

Although BMI is often used as surrogate for adiposity, it merely provides insight into the proportion of weight to height, and does not actually capture body composition (i.e. fat mass versus lean body mass). In fact, the contributing compartments of the rapid weight gain observed during the first year change over time.

During the first four months, almost 40-45% of the gain in weight consists of body fat, whereas by age 2 years this has dropped to about 7%.[19] It is thought that the rapid fat deposition in early infancy probably represents a physiologic response to the high energy demands during the neonatal period, ensuring survival of the infant. The adiposity peak at around 6-9 months of age may be mainly attributable to an increase in fat cell size, whereas the subsequent increase in adiposity can be explained by increases in fat cell size as well as fat cell numbers.[23-25]

Regulation of growth in early life

Throughout fetal life, growth is dependent on maternal health, nutrition, and placental function. The main hormones influencing fetal growth are IGF-I, IGF-II, and insulin. IGF-I and IGF-II levels correlate with size at birth.

During early infancy, growth is thought to be mainly dependent upon nutritional status, but from the age of 6 months, hormonal influences become increasingly important. The rapid growth and associated changes in body composition during infancy and childhood are regulated by the growth hormone–insulin-like growth factor (GH–IGF) axis, which is susceptible to environmental influences, particularly nutrition[26,27] (**Figure 8**). Negative energy balance leads to lower plasma levels of insulin, IGF-I, leptin, ghrelin, and other

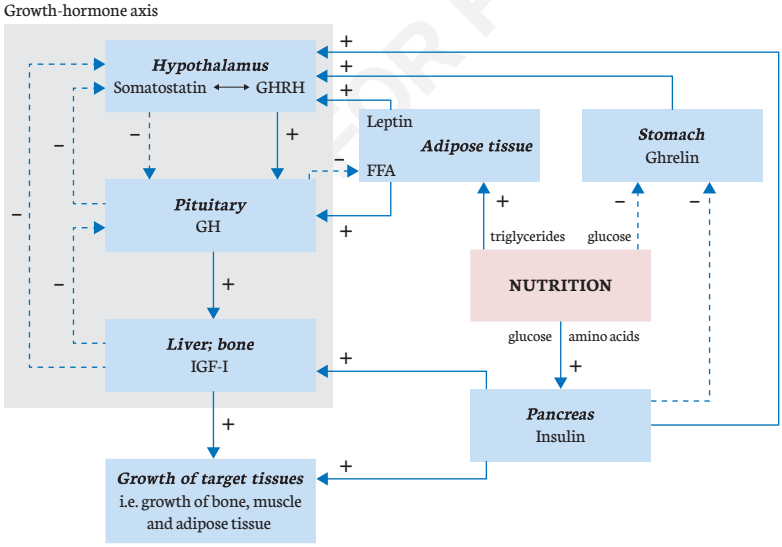


Figure 8. Effects of nutrition on hormonal regulation of growth[*,27,28,85–87]

FFA, free fatty acids; GH, growth hormone; GHRH, growth hormone releasing hormone; IGF-I, insulin-like growth factor-I.

*Schematic representation of the growth-hormone axis summarizing the currently known effects of nutrition on growth hormone regulation via different hormonal pathways.

hormones, and along with other systemic factors, these hormonal alterations have a direct effect on linear growth.[12,27] Optimal growth is thus dependent upon adequate nutrition and normal endocrine function, but it is also influenced by genetic constitution, a nurturing environment including (but not limited to) the absence of chronic disease, pollution, adequate hygiene and access to proper healthcare.[4,6]

The greatest effect of postnatal growth-modifying factors tends to be observed during infancy, due to the rapid growth and distinct changes in body composition that occur during this period.

Fetal factors influencing postnatal growth

Birth weight-for-gestational-age is often used as a surrogate for fetal growth. The growth rate in early postnatal life is known to be strongly dependent on birth weight; smaller infants tend to display catch-up growth,[11,29,30] while heavier infants tend to show catch-down growth.[31,32] Clinically significant catch-up growth is usually defined as a weight or length gain of greater than 0.67 standard deviation scores during the first two years, while catch-down growth is usually defined as a decrease of more than 0.67 standard deviations scores.[33–35]

In term-born infants, fetal growth during the last trimester of pregnancy is, like birth weight, inversely associated with early postnatal weight gain.[11,29,30,36] In healthy pregnancies, the slight slowing of growth is known as maternal restraint, a phenomenon that reduces the risk of birth complications. However, such associations may be directly affected by the postnatal environment; for example, when sub-optimal nutritional conditions do not allow for catch-up growth, low birth weight is often a strong predictor of stunting through to two years of age.[29]

Body composition at birth varies widely;[37] for example, in one study, up to a four-fold difference in neonatal fat mass (5%-20%) was observed between infants with comparable birth weights.[38] One important driver of birth weight, neonatal adiposity, and the postnatal growth

trajectory is gestational age, highlighting the importance of using specific parameters such as weight-for-gestational-age when evaluating an infant's birth weight. Infants born before term (<37 weeks + 0 days) show lower body fat levels; the effect of preterm delivery on postnatal growth trajectories and body composition will be discussed separately (**Chapter 4**).

The influence of gender on growth

Distinct gender differences in postnatal weight gain, linear growth, and adiposity development are apparent,[16] with female infants tending to grow more slowly than male infants during the first six months.[30,39] This explains the need for standardized sex-specific growth charts[16] (see WHO Child Growth Standards, available at: http://www.who.int/childgrowth/standards/technical_report/en/index.html). Male infants also show differences in body composition development (e.g. higher fat-free mass and lower total and subcutaneous adiposity) compared with female infants.[19,40-42]

These differences in body composition are also directly linked to the response to environmental influences.[43,44] Growth trajectories of male and female infants are differentially affected by the mode of infant feeding.[43,44] For instance, one study demonstrated that breastfeeding more strongly protects against childhood overweight in boys born to overweight mothers than in girls born to overweight mothers.[44] In another study, formula-fed girls showed greater length-for-age gain than their breastfed counterparts between 6 and 12 months of age, but this pattern was not evident in boys.[43]

Parental and lifestyle factors influencing growth

Although parental ethnicity may influence growth and adiposity of the offspring in early life,[45] most of this influence disappears when controlling for environmental factors such as dietary and socioeconomic conditions.[4,6,16,46] In low-to-middle income countries, for

instance, a higher household income is associated with increased infant growth rates and a lower risk of growth stunting;[47] in contrast, in high income countries, a *low* maternal education or socioeconomic status is associated with increased infant weight gain in the first year, and higher susceptibility to obesity.[48-50] Hence, when minimizing adverse environmental influences, infants and children across the globe can achieve similar growth potential.[51] This is well illustrated by the high degree of similarity in linear growth among ethnically diverse populations in the large international study upon which the WHO growth reference charts are based (discussed below).[51]

While length at birth correlates poorly with parental height, at around 2 years of age following a period of catch-up or catch-down growth, correlation with parental height improves.[27] Maternal and paternal heights appear to be positively associated with weight growth velocity in early infancy.[39]

Impact of infant feeding mode

It is well established that breast milk is the ideal nutrition source to support optimal growth and cognitive development in infants,[4] and, as discussed in **Chapter 1**, the **WHO recommends that infants are exclusively or predominantly breastfed for 6 months, with introduction of appropriate complementary foods at around 6 months of age, along with continued partial breast-feeding for at least 12 months, but preferably up to 24 months**. Infants fed according to this practice tend to show a highly predictable pattern of growth.[4,6,16,46,52,53]

Breast- and formula-fed infants show a marked divergence in growth during infancy.[36] The majority of studies show that breastfed infants tend to achieve faster weight-for-age and length gains in the first 1-4 months after birth,[4,10,30,36,54] with an earlier infant BMI peak and slower pre-peak velocity,[13] compared with formula-fed infants. This early

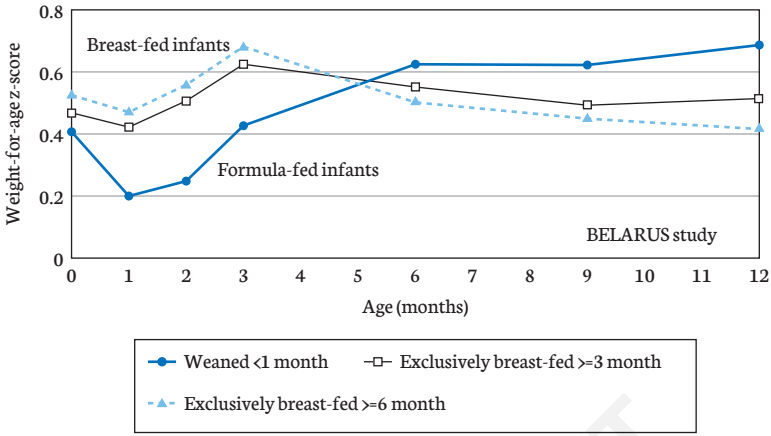


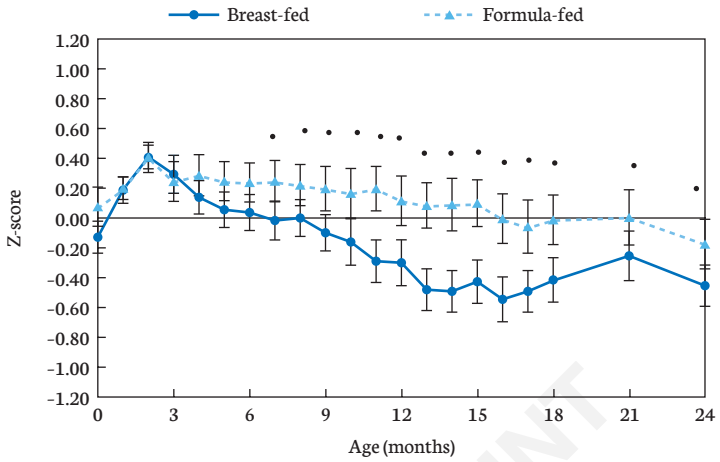
Figure 9. Weight-for-age changes in breast- versus formula-fed infants during the first 12 months of life[54]

Adapted with permission from: Kramer et al. *Pediatrics* 2002;110:343-347. Weight-for-age z-scores were based on the WHO/CDC reference standards.[54]

rapid growth in breastfed infants is followed by slower growth gains in later infancy, which may persist through the first 2-3 years.[4,10,30,36,44] In contrast, formula-fed infants show an initially slower, but continuous increase in weight during the first six months resulting in higher ultimate weights at that age[30] (see **Figures 9** and **10**). This greater weight-for-length is characterized by larger skinfold thicknesses between 9-15 months compared with breastfed infants, and formula fed infants tend to remain heavier with a higher body fat percentage throughout the first two years.[55,56]

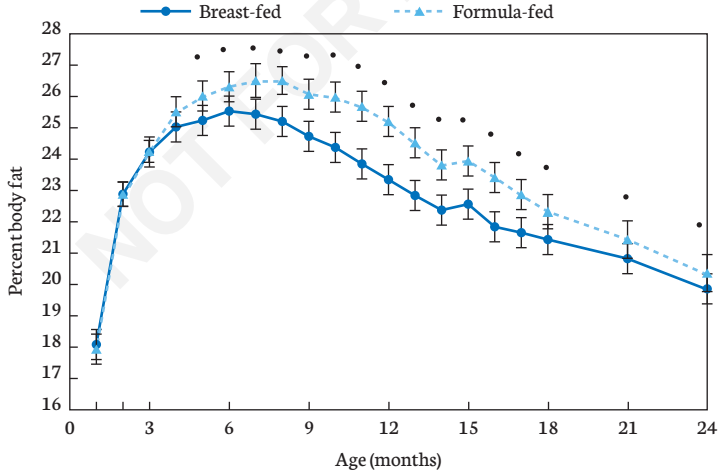
It should be noted that studies of breastfeeding patterns and infant growth are only based on observational, rather than randomized studies, often relying on maternal recall or limited by multiple confounding factors.[1] However, the length and exclusivity of breastfeeding do appear to consistently influence postnatal growth. Prolonged and exclusive breastfeeding tends to maintain slower late-infancy growth rates for longer;[54,57] and, in infants with a high birth weight and/or those who show rapid early growth, prolonged and/or

A) Weight-for-length*



Weight-for-length *Z* scores ($\bar{x} \pm$ SE) of breast-fed (n = 41–46) and formula-fed infants (n = 35–41). *P < 0.05.

B) Percentage body fat†



Percent body fat ($\bar{x} \pm$ SE) of breast-fed (n = 41–46) and formula-fed infants (n = 35–41). *P < 0.05.

Figure 10. Changes in A) weight-for-length and B) percentage body fat in breast- versus formula-fed infants during the first 24 months after birth[55]

Adapted with permission from: Dewey et al. *Am J Clin Nutr* 1993;57:140-145.

*Z-scores for weight-for-length were calculated using National Center for Health Statistics reference data, based mainly on formula-fed infants.

†Percentage body fat was estimated using a prediction equation calculating percent body fat based on five skinfolds.

exclusive breastfeeding appears to offer moderate protection against later excess childhood fat accumulation[1,58] – particularly in male infants, as described above.[44]

Increasing evidence supports the concept that the typical growth pattern as observed in breastfed infants may be the most optimal growth pattern with regard to the development of well-balanced body composition and prevention of later overweight (see **Figure 11**), as well as adverse health outcomes in later life.[10,13,57,59]

> Increasing evidence suggests that the typical growth pattern observed in breastfed infants may be the most optimal growth pattern with regard to the prevention of overweight and adverse health outcomes in later life.

This nutrition-dependent difference in growth patterns is thought to be partly related to differences in quality and composition of breast

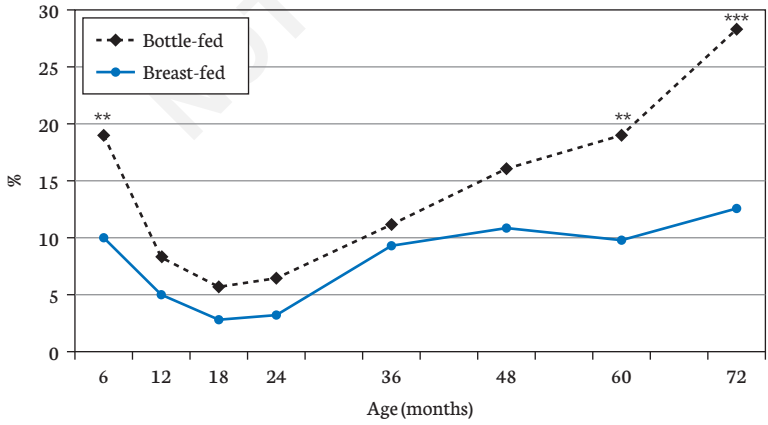


Figure 11. Prevalence of overweight (>90th percentile of BMI reference values) in the first six years of life for breast- versus formula-fed infants[60]

Adapted with permission from: Bergmann et al. *Int J Obes.* 2003;27:162-17.

Table 5. Composition of mature human milk versus infant formula

Mean value for component (per litre)		
	Mature human milk[a]	Infant formula[b]
Energy (kJ)	2,929	2,500–3,550
Energy (kcal)	700	597–848
Protein (g)	10.3	11–24.8
Fat (g)	43.8	26–53
Carbohydrate (g)	68.9	72–75
Sodium (mg)	170	125–532
Calcium (mg)	320	min 300
Phosphorous (mg)	140	150–887
Iron (mg)	0.3	5–17.7
Vitamin A (mcg)	610	350–1526
Vitamin C (mcg)	50	min 42.5
Vitamin D (mcg)	1.0	625–22.3
Potassium (mg)	510	500–1775

[a] US Department of Agriculture (USDA) National Nutrient Database for Standard Reference 2011.[195]

[b] Ranges for infant formula products (from birth, cow's milk-based) based on the regulatory minimum, and, where given, maximum range permitted. Adapted from: FSANZ Code Standard 2.9.1.[197]

Reproduced with permission. Infant feeding guidelines: Information for health workers. Canberra: National Health and Medical Research Council. 2012. Available at: *https://www.nhmrc.gov.au/guidelines-publications/n56*

versus formula milk (see **Table 5**), and partly due to differences in total nutritional intake patterns over time.[30,55] Other potential confounding factors might include feeding behaviors, timing of the start of complementary feeding, composition of the weaning diet (protein quantity and quality; fat content), health status, and maternal and lifestyle factors.

Complementary feeding and impact on growth

The period between approximately 4-6 months through 24 months when complementary (solid or semi-solid) foods are first introduced

into the diet is crucial for establishing and maintaining an appropriate growth trajectory.[61,62]

Timing

In terms of growth trajectories, whether 4 or 6 months is the ideal age for introduction of complementary foods is controversial, but no adverse effects on growth (including obesity) have been consistently demonstrated for either time point.[61] Some evidence does suggest that very early introduction of solid foods (<3-4 months) may increase the risk of weight gain and/or childhood adiposity/obesity, particularly in formula-fed infants[61,63,64] or in infants breastfed for only a short duration (<20 weeks).[61] Infants weaned later (≥6 months) from breast or formula milk show a slower overall growth rate and smaller size (lower weight-for-age) at 6 months of age compared with infants introduced earlier to solid foods.[57]

As well as the postnatal growth trajectory, other important outcomes that may be influenced by the timing of complementary food introduction include the timing of breastfeeding cessation (premature cessation should be avoided); food allergy risks; and the relationship between early exposure to new tastes and later increased food acceptance. In low-income countries, earlier introduction to complementary foods may also increase the risk of contamination and infection.

Dietary composition

The WHO recommends that breastfeeding should be continued while introducing solids,[62] as explained above.

During the complementary feeding period, the infant transitions to consuming a variety of food types and textures while needing to satisfy relatively high nutrient requirements.[61] A lack of appropriate nutrient-dense (but not energy-dense) foods during this period

may contribute to the increasing nutrient gaps that have been reported, for instance, among toddlers in Europe.[65]

Evidence for best practice in complementary food introduction is unclear, as the available data is mostly observational, and most studies do not control for previous or concurrent breast- or formula-feeding practices.[61] It is known that differences in weight patterns observed in breastfed versus formula-fed infants persist after complementary foods are introduced.[66]

A diet composed of an increasing variety of foods is required to ensure that all the infant's nutritional needs are met,[62] and to help the infant learn to accept a variety of flavors and textures. Appropriate food texture and consistency, feeding frequency, and energy intake should be suited to the age and development of the infant.[62,67,68] To ensure optimal growth and development, complementary feeding frequency and energy intakes should ideally not exceed the recommended levels, to avoid impairment of breast milk intakes,[68] and food preparation methods should minimize the risk of contamination with pathogens.[62]

Although high protein intake has been cited as a risk factor for excessive weight gain during the complementary feeding period and beyond, the impact of total protein in the weaning diet on growth is debatable.[61,69,70] Some evidence suggests that a high total protein intake (as a percentage of total energy intake) during the first two years of age is positively associated with height velocity and fat mass,[69-72] and it has been suggested that it may be prudent to avoid high protein intakes in children under two years to help prevent the later development of overweight and obesity.[70] Other evidence suggests that the *type* of protein (i.e. protein quality) appears to be more important than the total protein concentration

per se; mainly dairy protein (rather than meat protein) appears to promote higher growth rates.[61]

Fat intakes also appear to be associated with body fat development in some studies, but not in others.[61,72,73] One review has shown no convincing evidence of an association between dietary fat intakes between 6-24 months of age and later adiposity or adverse health conditions,[73] and one study showed that a higher fat intake at two years of age (as a percentage of total energy) was actually associated with *lower* skinfold thicknesses in adulthood.[74] However, specifically in cases of excessive weight gain during the toddler period (after 1 year of age), it has been suggested that a carefully selected lower fat intake (i.e. a reduction in saturated fats, but not in polyunsaturated fatty acids) may be an appropriate intervention to reduce overall energy intake.[61,72] However, low total fat intake has also been associated with an increased risk of later overweight[74] (see **Chapter 8**), indicating a delicate balance between the quantity and quality of fat in the diet.

Also relevant to note is that inadequate levels of micronutrient intakes can affect growth. In particular, it is important to ensure that iron and zinc intakes are adequate.[61,67]

Other factors

Several other factors have been implicated in the modulation of postnatal growth. A summary of known or possible growth-modifying factors is provided in **Table 6**. Factors that are specifically associated with stunting/wasting and obesity are discussed in detail in **Chapters 7** and **8**, respectively.

Growth monitoring measures

Healthcare professionals involved in the care of infants and toddlers rely heavily on objective assessments of growth to determine if a

Table 6. Some factors suggested to be associated with postnatal growth

Growth-modifying factor	Positive (+) or negative (–) association with weight gain velocity (weight-for-age, unless otherwise specified)
Prenatal factors – Gestational	
Smaller fetal weight gain during 3rd pregnancy trimester[11]	+
Prenatal factors - Fetal	
Birth weight*†[30,36]	– (first 6 mo) + (12-24 mo)
Female gender*[30,39]	–
Prenatal factors – Maternal/Paternal	
High maternal BMI*§¶[39,75]	+
High paternal BMI*†[30,39]	+/– (data vary)
Low maternal birth weight[76]	–
Parental heights (particularly paternal height)*[39,77]	+
Higher gestational weight gain¶[39,78,79]	+
High maternal plasma glucose concentration¶[39]	–
Increased parity*†‡[30,39]	–
Nutritional factors	
Breastfeeding (vs. formula feeding)[4,10,30,36,39]	+ (first 1-2 mo) – (after 2-12 mo)
Combined breast/formula feeding†§[30]; formula-feeding only[29]	+
Later weaning (around 6 months versus <4 months)[57]	–
Timing of complementary food introduction and dietary composition†§[30,61]	+/– (depends on food selection and early (<4 mo) vs later (≥6 mo) introduction)
Infant undernutrition[12]	–

(continued on next page)

Table 6. (continued)

Growth-modifying factor	Positive (+) or negative (–) association with weight gain velocity (weight-for-age, unless otherwise specified)
Socioeconomic factors	
Low family income[47]	–
Higher maternal educational level[‡30,48]	+/– (data conflict, socioeconomic development-dependent)
Infant lifestyle factors	
More hours of sleep (infants)[†‡ 30,80]	– (lower obesity risk[80])

mo, months
*influences growth during the first 6 months of life
†influences growth between 6-12 months
‡influences growth between 12-24 months
§associated with weight-for-length, rather than weight-for-age
¶possible 'fading' influence over the first 3 months of life[39]

child's physiological needs for growth and development are being met, and particularly to establish whether nutrition is adequate.[46,81]

Accurate, reliable serial weight and length/height measurements throughout childhood, and in addition head circumference measurements in infants and toddlers up to 2 years of age, are fundamental to growth monitoring and clinical decision-making based on growth patterns.

Growth assessments should be:[4,5]

- Performed routinely during regular healthcare visits; for example, assessments might be performed in tandem with a national immunization schedule

- Measured accurately by trained staff, using calibrated, well-maintained equipment and standardized measurement techniques
- Plotted accurately on an appropriate sex-specific growth chart
- Correctly interpreted, in conjunction with other general health information
- Used as a prompt to initiate action, including referral, when necessary
- Explained and discussed with the child's family, including the importance of positively reinforcing healthy nutritional and lifestyle practices

A wide range of national postnatal growth references are available worldwide, which are based on varied, populations with different criteria and definitions of underweight, overweight, and obesity,[6,46] and which may be either suitable for term infants, or specific for preterm infants (e.g. the Fenton charts,[82,83] discussed in **Chapter 4**). Healthcare professionals often use such reference charts with a limited appreciation of the quality of the population and study design that generated the charts.[6] Notably, some recent national growth chart curves have reflected the increasing prevalence of childhood overweight, leading to under-identification of overweight infants and children, and over-identification of infants and children with failure-to-thrive.[4,10] Local nutritional status, feeding practices, and health issues also have potential to skew the data.[10]

> Accurate, reliable, serial weight and length/height measurements in all children, and head circumference measurements in infants and toddlers … are fundamental to growth monitoring and clinical decision-making based on growth patterns.

Considerations when interpreting growth charts

There are several important considerations for interpreting a child's measurements against a growth chart:[4]

- Assessment of infant and early childhood growth involves considering the *overall trajectory* of weight-for-age, length/height-for-age, weight-for-length, and head circumference.
- Single measurements are of little value; serial measurements are needed to describe a child's growth.
- Generally, centile positions of the different anthropometric measures should not deviate markedly in a healthy child; a large difference in one measurement relative to the others may indicate a potential problem or a measurement error.
- The 50th percentile is not the norm or goal for each individual child. The tracking of serial measurements relative to normal centile curves is more important than the actual percentile.
- Some deviations in a child's growth curves are normal, particularly if regressing toward the 50th centile, rather than away. Major deviations, such as crossing two centile lines or a deviation away from the mean, may indicate an abnormality and warrants further evaluation.
- The feeding method (breast or formula) should be considered when assessing the growth of infants during the first few months following birth. Acknowledging the differences between formula- and breastfed infants helps avoid unnecessary interventions to increase or limit nutritional intakes or change the mode of feeding.

In addition, as discussed above, anthropometric growth charts do not reflect body composition development, although infant body composition and the implications for programming of health outcomes is an active area of health research. Assessment of the success of nutritional interventions in compromised infants may be improved by measuring changes in fat-free mass versus fat mass.[40]

As a starting point, normative data must be established, but data are scant, and derived from a variety of different assessment methods.[40]

Growth charts should ideally be based on longitudinal data.[4] They should also ideally be representative of healthy children fed according to recommended practices, particularly breastfeeding practices;[4] this is a key benefit of the WHO international growth standards, as discussed below.

Growth charts should ideally be based on longitudinal data, and should be representative of healthy children fed according to recommended practices, particularly breastfeeding practices.

WHO growth standards

In 2006, the WHO published a set of international growth standards for children from birth to the age of 5 years, based on the Multicenter Growth Reference Study (MGRS) data. The charts were constructed exclusively from data obtained from healthy, full-term infants with no detectable mal-, under- or over-nutrition, born to mothers who had no socioeconomic constraints and who did not smoke during or after pregnancy. All infants were breastfed according to current recommendations – i.e. exclusively or predominantly breastfed for 4-6 months, with introduction of complementary foods around 6 months of age, and with continued breastfeeding until at least 12 months of age.[10,16] The study combined longitudinal data from children aged 0-24 months, and cross-sectional data from children aged 18-71 months.[16]

Because all children in the study were raised under optimal health conditions, and breastfed according to current recommendations, the

WHO growth standards are considered to be a useful global benchmark against which to measure growth during the first years of age.[4,16,46] Patterns of linear growth demonstrated in the data set were remarkably consistent between the six participating countries (Brazil, Ghana, India, Norway, Oman, and the USA), and were validated in four other countries (Maldives, Pakistan, Argentina, and Italy), suggesting that the WHO standards are an effective reference model for detecting both under- and over-nutrition in ethnically diverse populations.[4,6,16,46]

Nevertheless, there is ongoing debate as to the utility of the WHO growth standards in *all* populations. For example, the MGRS study had limited data input from Asia, and no data from East Asia, so the relevance and/or potential limitation in use of the WHO standards for Asian populations is unclear.[46] In addition, because the WHO growth charts are based on term infants only, they are unsuitable for the assessment of preterm infants. Specific growth charts for preterm infants are discussed in **Chapter 4**.

Global implementation

Despite differences among some specific infant populations, the WHO growth standards reflect generally expected growth patterns for healthy infants and children when their nutritional and environmental health needs are optimally met,[4,10] and it has been suggested that increasing implementation of these standards will allow greater global consensus and standardization of screening, referral, and intervention for at-risk infants.[10,46] To date, the WHO standards are at varying levels of implementation in more than 110 countries.[10,46] Notably, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommends that the WHO child growth standards be used to monitor all children in Europe from birth to 2 years of age, including both breast- and formula-fed infants.[46] Monitoring children up to the age of 5 years against the WHO standards is also advisable.[46]

The WHO growth standards reflect expected growth patterns for healthy infants and children, and it has been suggested that increasing implementation of these standards will allow greater global consensus and standardization of screening, referral, and intervention for at-risk infants.

WHO child growth standards charts (length-for-age, weight-for-age, weight-for-length, and BMI-for-age)

Download free from:

www.who.int/childgrowth/standards/Technical_report.pdf

The WHO has developed a comprehensive set of free software for personal computers and mobile devices, related to the WHO international growth standards.

Download free from:

www.who.int/growthref/tools

Use of BMI charts in infants

While some national growth charts (e.g. Centers for Disease Control [CDC] charts) use BMI charts from the age of 2 years, the newer WHO standards include BMI-for-age charts starting from birth. The value of using BMI charts to evaluate infants from birth is not entirely clear,[4,5] particularly as there are some ethnic variations in infant BMI.[45] However, one clear advantage is that, after the infant BMI peaks around 6-9 months of age,[21] an increase or decrease in BMI may help predict body composition development patterns in relation to obesity risk.

As discussed above, infants undergo dramatic changes in body composition during the first year, and accurate measurements of body length are difficult to obtain in infants, who often resist full leg extension and rarely lie still. Moreover, when an infant is identified by BMI as being overweight or obese, current recommendations for infants would not support dietary restriction because of the potential negative impact on linear growth and brain development.

It is therefore recommended that BMI charts be used with caution in children under the age of 2 years. Traditional measures, such as weight-for-length, should continue to be used until the validity of using BMI data in infants and young children is fully established.[4,5]

More detailed body fat measures than can be described by BMI alone may also improve the prediction of later overweight and cardiovascular risk factors. While more detailed measurements are not used in everyday clinical practice, research suggests that abdominal skinfold thickness (indicating a higher level of abdominal subcutaneous fat) tends to track more strongly from infancy through 6 years of age than preperitoneal fat mass measures, and appears to be a stronger predictor of cardiovascular risk factors during childhood.[84]

> Although it is recommended that BMI charts be used with caution in children under the age of 2 years, and that traditional measures, such as weight-for-length, continue to be used until the validity of using BMI data in infants and young children is established, BMI development after the peak around 6-9 months of age can be predictive of later obesity risk.

Chapter highlights

- Adequate serial growth monitoring in infancy and early childhood is essential to ensure timely and proper intervention in cases of growth deviations. The WHO has published a set of international growth standards for children from birth to the age of 5 years that have become widely accepted as suitable charts in any given country worldwide.
- From birth to the age of 2 years, a child's weight increases fourfold. At 2 years, a child has reached approximately 50% of their expected adult height, approximately 90% of their expected adult head circumference.
- Directly after birth, most infants experience an initial weight loss, followed by high growth velocity in the following 3-4 months. BMI typically peaks at around 6-9 months of age, and after 12 months relatively more investment is in length gain, resulting in a decline in BMI until 5-7 years of age. The decline in BMI and subsequent rise after birth is termed an 'adiposity rebound', and is followed by a second, slower increase in adiposity at the onset of puberty.
- Postnatal growth rates are strongly dependent upon birth weight; smaller infants tend to display catch-up growth, while heavier infants tend to show catch-down growth.
- Although parental ethnicity may influence growth and adiposity of the offspring in early life, most of this influence disappears when controlling for environmental factors such as dietary and socioeconomic conditions.
- Breast- and formula-fed infants show some divergence in growth during infancy. It is well established that breast milk is the ideal nutrition source to support optimal growth and cognitive development in infants, and increasing evidence suggests that the typical growth pattern observed in breastfed infants may be the most optimal growth pattern with regard to the prevention of later overweight and adverse health outcomes.

- As well as the milk feeding period in early infancy, the period between approximately 4-6 months through 24 months when complementary foods are introduced into the diet is crucial for establishing and maintaining an appropriate growth trajectory.

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SECTION B

Compromised birth

Chapter 4

Growth in preterm infants

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Definitions

At birth, neonates are classified by gestational age (preterm versus term), by birth weight, or by weight for gestational age (**Figure 9**).[1] Depending upon the classification, overlaps between term and preterm populations are possible.

By applying these different neonatal definitions, various compromised birth groups can be defined. These are discussed in this, and the following two chapters.

Classification according to birth weight

Neonates with low weight at birth – either born at term or preterm – may be classified as low birth weight (LBW; <2,500 grams), very low birth weight (VLBW; <1,500 grams), or extremely low birth weight (ELBW; <1,000 grams) (**Figure 12**).[1–4]

Classification by gestational age

A term infant is born with a gestational age between 37 weeks + 0 days and 41 weeks + 6 days. An infant is classified as post-term when born at or after 42 weeks + 0 days of gestation. Preterm infants are generally defined as those born before completion of 37 weeks of gestation.

Preterm infants can be further classified as extremely, moderately, or late preterm. Classifications vary; for example, the WHO definition of a late preterm infant is one born with a gestational age between 32 weeks + 0 days and 36 weeks + 6 days, whereas other institutions use a range of 34 weeks + 0 days to 36 weeks + 6 days.[5,6]

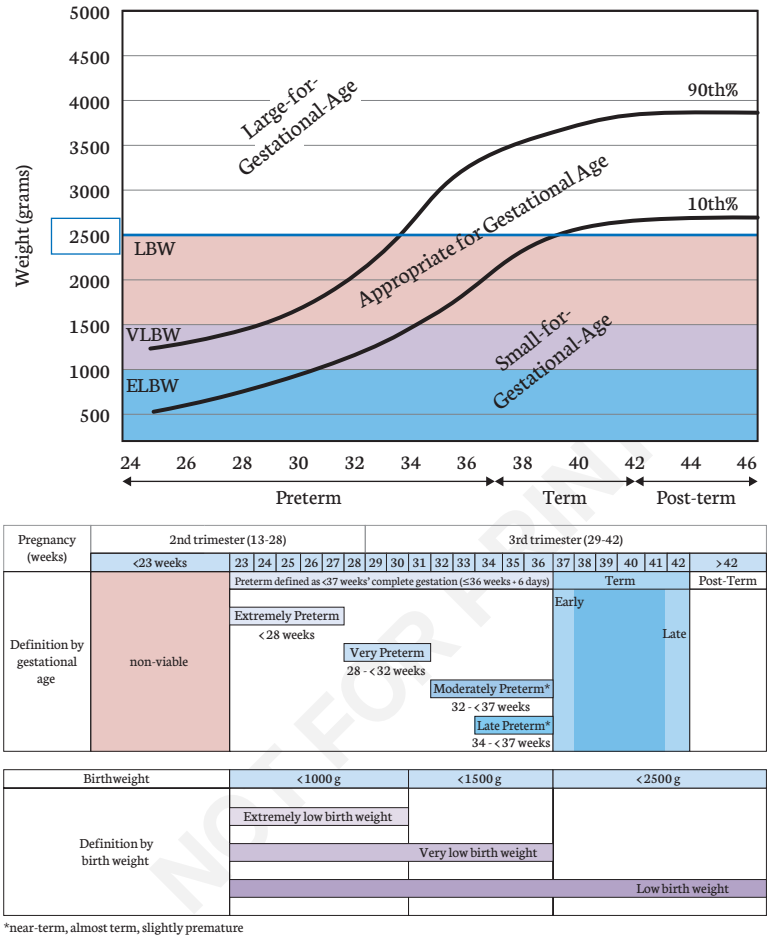

Figure 12. Classifications of preterm infants according to gestational age or birth weight[7,8]

Adapted with permission from: Engle WA. *Seminol Perinatol.* 2016; 30:2-7

Graph is based on a hypothetical median weight of 2500 g. Classification cut-off weights are indicative only, and will vary based on infant gender and the reference standard used.

Classification by size for gestational age

Infants classified according to gestational age are grouped into three categories: "appropriate-for-gestational-age" (AGA), SGA, and LGA. This classification is applicable to both term and preterm infants.

Infants born AGA are those whose birth weights fall between the 10th and 90th percentiles on applicable growth charts of the weight expected at that particular gestational age.[9]

Infants classified as SGA are born with a birth weight lower than the 10th percentile for their gestational age. LGA infants are generally defined as those with a birth weight greater than the 90th percentile for gestational age.[9] These classifications are universally agreed. Some studies report on the SGA population as those with a birth weight below the 20th percentile for their gestational age; this definition, while inappropriate in clinical practice, may still be useful for specific research purposes. Term SGA and LGA infants will be discussed in **Chapters 5** and **6**, respectively.

In this chapter, we discuss the prevalence of preterm birth, along with risk factors, assessment methods, nutritional interventions, and short- and long-term prognoses.

Prevalence of preterm birth

More than 10% of infants worldwide are born prematurely, amounting to approximately 15 million preterm births each year.[10,11] Preterm birth is a global problem affecting both low- and medium income as well as high income countries, with national rates ranging from 5% to 18%.[11]

Lower-income countries tend to have slightly higher rates compared with higher-income countries. More than 60% of all preterm births occur in Sub-Saharan Africa and South Asia, but the United States and Brazil are also among the 10 countries with the highest numbers.[10]

In almost all countries with reliable data, the rate and burden of preterm births are increasing,[9-12] mostly due to an increase in numbers of late preterm births.[12]

Infant survival

The survival of preterm infants worldwide has greatly improved during the past few decades, largely due to improvements in obstetric and neonatal care.[2] More than 80% of all preterm births occur between 32 and 36 weeks + 6 days gestation, and the majority of these infants can survive with specialized care.[9,10] Especially in highly specialized neonatal intensive care units (NICUs), infants born as early as 23 weeks' gestational age are able to survive.

However, 1.1 million infants worldwide still die from preterm birth complications each year, with the highest risk of neonatal death due to preterm delivery observed in countries where adequate neonatal care is lacking.[9,10] The WHO has reported that, without access to advanced medical support, infants born at 34 weeks' gestational age in low-to-middle income countries have only a 50% survival rate.[10] Preterm birth is the single largest global cause of death within the first month after birth.[10]

Risk factors for preterm birth

While most preterm births occur spontaneously with no identified cause, early induction of labor and cesarean birth are also major contributing factors, in particular to late preterm births.[10]

A variety of factors may contribute to the risk of preterm delivery, including those listed below (**Table 7**).

Based on identified risk factors, evidence is increasing that maternal health and nutritional status before pregnancy are crucial factors contributing to the risk of preterm birth. Notably, a recent study indicated that an established prenatal dietary pattern containing fruit, vegetables, some whole grains, and several protein-rich food sources is associated with a reduced risk of preterm delivery. In contrast, dietary patterns associated with consumption of high-fat, high-sugar foods

Table 7. Summary of pre-conception and pregnancy/birth risk factors associated with preterm birth, based on selected reviews from the literature

Pre-pregnancy/maternal factors	Factors during pregnancy/birth
• Adolescent age[10,13] • No prior pregnancies[10,13] • Multiple pregnancies (twins, triplets, etc.)[10] • Short interval between births[10] • Maternal under- or overweight[10] • Chronic conditions e.g. diabetes, high blood pressure[10] • Genetic predisposition[10] • Infectious diseases e.g. sexually transmitted infections[10] • Poor nutrition[14] • Low income[10]	• Infectious diseases[10] • Substance abuse (e.g. tobacco; heavy alcohol consumption)[10] • Poor nutrition[10,14] • Poor psychological health affecting maternal care and nutrition[10] • Exposure to environmental risks e.g. indoor air pollution[10]

CRH, corticotrophin releasing hormone

and frequent consumption of 'takeout' foods was associated with an increased risk of preterm delivery.[14]

Implications and prognosis

Preterm infants are a particularly vulnerable group because they are immature at birth, meaning that key steps in maturation need to take place outside the mother's womb. Accelerated tissue growth and key steps in the development of functional maturity takes place in the last trimester of pregnancy, particularly for the brain, lung, gut, bones, immune system, and adipose tissue. Infants born before term miss out on essential parts of this vital developmental window of opportunity.[5,16,17] Even late preterm birth, where infants miss only around three weeks of intrauterine growth, may have substantial short- and long-term implications.[5,12,16]

Childhood consequences of preterm birth

Infants who were born prematurely face the challenge of completing their development *ex utero,* which may have lifelong health consequences.

1. Growth faltering

Some preterm infants are born SGA and thus have already experienced growth restriction *in utero*; higher numbers of preterm SGA infants are found in countries with poor maternal health.[10] In addition, there is strong evidence that preterm infants have a higher risk of growth faltering in the first two years after birth,[12,18] the risk being inversely associated with gestational age.[19] Given the high nutritional needs for growth, with a simultaneous immaturity of the gut and other metabolic organs, preterm birth can be seen as a state of nutritional emergency.[20] Consequently, growth faltering often occurs soon after birth, and preterm infants who accumulate growth deficits during their hospital stay may be discharged with growth (most often defined as weight-for-age) below the 10th percentile.[21,22]

Growth faltering is particularly prevalent among extremely preterm infants who experience major perinatal morbidities such as necrotising enterocolitis, bronchopulmonary dysplasia, brain damage, or sepsis.[21] These major postnatal complications may even drive increased nutritional needs, but are often accompanied by feeding intolerance and poor growth, which in itself further compromises optimal organ growth and development. Early detection of growth faltering is important to ensure that optimal nutritional support is started as early as possible, since it may be difficult or impossible to recover from accumulated nutrient deficits.[19,22]

2. Neurodevelopmental impairment

Impaired neurodevelopment has become the primary morbidity outcome of interest in infants born prematurely.[17] In the final trimester of pregnancy, the brain undergoes a remarkable process of growth and differentiation; following premature birth, brain development

continues to progress for the next two years and beyond, but is highly vulnerable to insults such as nutritional insufficiency or hypoxic ischemic insults.[17] Many preterm infants accumulate nutritional deficits in the first few weeks after birth,[22] placing them at increased risk of childhood neurodevelopmental impairments, e.g. learning disabilities, hearing/visual problems, and behavioral problems.[1,5,10,16]

In terms of growth markers, impaired early postnatal head growth (measured by head circumference, a crude estimate of brain growth) and inadequate weight gain appear to be associated with long-term neurological and cognitive deficits in children.[3,23,24]

A variety of prognostic factors may be associated with neurodevelopmental outcomes, including gestational age, size for gestational age, brain damage (e.g. intracranial hemorrhage), socioeconomic status, and infections;[17] the relative importance of each factor however, is unknown.[3]

Consequences in adulthood

Preterm infants are often born with (very) low birth weight, and despite a tendency toward rapid postnatal catch-up growth when nutrition is adequate, are at increased risk of early stunting.[12] While rapid catch-up growth confers several potential short-term advantages in terms of survival and more favorable neurodevelopmental outcomes, it is also associated with a possible increased risk of metabolic disorders in later life, including hypertension, insulin resistance, and cardiovascular disease.[1,12,16,23] Appropriate weight gain should nevertheless be encouraged in preterm infants, to ensure infant survival and optimal growth and neurodevelopmental outcomes.[25,26]

> Preterm infants are at increased risk of growth faltering related to neonatal morbidities and feeding challenges, which places them at high risk of long-term health problems.

Assessing postnatal growth in preterm infants

Preterm infants need to undergo regular growth assessments.[21,27] Growth goals for preterm infants mimic estimates for fetal growth rates,[27] although this may not be possible in all cases as the extrauterine environment differs strongly from the intrauterine environment. A rapid increase in weight after birth may, for instance, reflect fluid accumulation rather than tissue accretion; the cause thus needs to be evaluated and managed accordingly.[28]

Although international growth charts are available from the WHO, (see **Chapter 3** and **Appendix**), these depict weight, length, and head circumference development for the *term* infant population, and do not cater to preterm growth assessments *before* term corrected age.[27]

Several other growth charts are being used worldwide to monitor growth trajectories in preterm infants after birth. One of the most well-established sets of postnatal preterm growth charts are the Fenton charts.[27,29] These charts are based on an international meta-analysis of six large population-based surveys involving a total of almost 4 million preterm infants.[27] The charts are specific for expected body weight, length, and head circumference growth patterns in infants born from 23 weeks' gestation onwards,[27] and are designed to link with the WHO infant growth standards around 50 weeks' gestational age.[27]

In **Chapter 2**, we discussed the INTERGROWTH-21st standards for fetal growth.[30] Postnatal growth charts specific for preterm infants were also published in 2015 as part of the INTERGROWTH-21st project.[31] It is expected that these newer charts will be used more frequently; although the study population was much smaller than that of the Fenton study. These and the Fenton charts are available free for download, and selected charts are located in our **Appendix**.

INTERGROWTH-21st preterm growth charts

(length-for-age; weight-for-age)

Download free from:

https://intergrowth21.tghn.org/articles/new-intergrowth-21st-international-postnatal-growth-standards-charts-available/

Fenton preterm growth charts

(length-for-age; weight-for-age)

Download free from:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3637477/

Proportional growth, rather than just weight gain, is also important in preterm infants during the postnatal period.[32] It is tempting in medical practice to consider "growth" as synonymous with weight gain. However, weight gain out of proportion to length gain (or head circumference) results in high weight-for-length infants, which may pose a risk with regard to metabolic development and increase risks in later life. Preterm infants often experience disproportionate growth after birth; for example, showing a high weight-for-length at hospital discharge, despite being small in terms of weight-for-age.[32] Thus, tracing weight-for-length, or using gender-specific BMI-for-age curves, such as are presented in a novel set of charts recently created by Olsen *et al* in the US,[32] may also be useful. The Olsen BMI-for-age charts are available in the **Appendix** to this book.

Proportional growth (weight-, length- and head circumference-for-age), rather than just weight gain, is important in preterm infants during the postnatal period.

Other measures of body composition, such as fat mass, fat-free mass, and bone mineralization may also be very important indicators of nutritional status in preterm infants trying to achieve appropriate catch-up growth.[16,33] However, these are more difficult to monitor in the routine clinical setting.

It should be noted that actual gestational age, gender, and hospital nutritional policies may influence catch-up growth patterns in the first few weeks after birth until discharge.[34]

Nutritional management to ensure optimal growth and development

Because key developmental steps need to take place in the extrauterine environment, preterm infants have an increased metabolic rate, and thus have increased nutrient requirements compared with term infants. These nutrient requirements are further increased as a result of limited endogenous nutrient reserves, metabolic instability,and disease and related medical interventions.

During the hospital stay

During the first week after birth, preterm infants, particularly VLBW and ELBW infants, may receive the majority of their nutrition via the parenteral route.[35] Lipid emulsions are used in parenteral nutrition as a low-volume source of energy and as a source of essential fatty acids.[36] The practice of initiating parenteral nutrition within hours of birth and parallel enteral feeding within hours to a few days is helping to increase overall nutrient intakes and reduce the risk of extrauterine growth restriction in preterm infants.[4,37]

The transition from parenteral to enteral nutrition is a critical period, and care should be exercised in calculating nutrient concentrations, to minimize any nutrient fluctuations during this transition, particularly with regard to protein.[4] A combined strategy of both enteral and parenteral nutrition (for instance, to provide specific amino acids[1,38]) is required to ensure adequate energy input from birth onwards.[19]

Human milk is always the best source of nutrition for an infant, and milk expression and feeding should commence as soon as possible, with maternal support to maximize milk production for later establishment of breastfeeding.[10,37] Early feeding with expressed human milk has been shown to reduce the risk of neonatal mortality in preterm infants.[10] If an infant's own mother's milk is not (yet) available, banked human milk is the preferred alternative.[39]

Preterm infants, particularly those born before 34 weeks' gestational age, may have difficulties latching, sucking, and swallowing, and may display less stamina for feeding. These factors, coupled with maternal stress or lack of support, may result in difficulty establishing successful breastfeeding.[40] Also, due to the high variability of nutrient content in human milk, as well as its decline in protein content over time, current recommendations recognize that human milk alone may not supply adequate protein, energy, minerals, and vitamins to support normal growth in preterm infants.[1,4] In such cases, ESPGHAN recommends fortification of human milk, or, if formula-fed, the use of a specialized preterm formula with higher protein-energy ratio, mineral, long-chain PUFA, and trace element contents, until at least term corrected age.[1,40]

> Human milk is always the best source of nutrition for both term and preterm infants. For the smallest preterm infants, human milk should be fortified to meet the infant's higher nutrient requirements.

Good nutritional support of preterm infants has been shown to improve neonatal growth and developmental outcomes.[21] It is well established that consumption of human milk is associated with improved brain development;[41] in addition, a randomized trial has demonstrated that feeding of preterm infants with a specific preterm formula was associated with improved cognitive performance at the age of 7-8 years, compared with a standard formula.[42] ESPGHAN

has published recommended ranges for enteral nutrient intakes for stable-growing preterm infants up to approximately 1,800 grams in body weight, based on scientific reports and expert consensus.[1]

Preterm infants have specific minimum energy requirements due to their unique physiology and metabolism.[43] While growth velocity and tissue composition comparable to normal intrauterine growth over this period is the goal,[38] greater fat deposition may be needed to provide thermal and mechanical protection in preterm infants.[1] However, overly rapid weight gain (for example, upward crossing of centiles) should be avoided as this has been shown to be related to adverse long-term risks.[1] Energy requirements for healthy preterm infants depend on differences in:[1]

- Post-conceptional age (younger post-conception age imposes higher energy requirements per kg body weight)
- Accumulated nutrient deficits during NICU stay
- Body composition
- Resting energy expenditure

Dietary lipids provide infants with most of their energy needs,[1,36] as well as essential fatty acids and lipid-soluble vitamins.[1] The amount, composition, and absorption of ingested lipids directly affect growth patterns and body composition.[1] Evidence suggests that, even when total energy intake is sufficient, protein intakes may be insufficient for preterm infants, especially those unable to cope with high feeding volumes. It has thus been suggested that optimal protein-energy ratios for preterm infants be re-appraised.[22]

For many other nutrients, specific requirements in preterm infants are unclear, although the prematurity of the metabolism may suggest a higher need for some nutrients. ESPGHAN and other groups,

including the AAP, have published guidelines for enteral nutrient supply specific to preterm infants, based on scientific data and expert consensus.[1,2,4]

Post-discharge feeding and monitoring

Goals of post-discharge nutrition are to continue (exclusive) breastfeeding, minimize and promptly address any nutrient deficits, and avoid over-nourishment and excessive growth acceleration.[40]

Evidence supporting the fortification of breast milk and the use of post-discharge formula in preterm infants after hospital discharge is scarce and conflicting.[4,24,40] A recent Cochrane review showed no growth benefits or neurodevelopmental benefits (the latter only in 2 studies) with breast milk fortification in preterm infants.[44] Another Cochrane review showed no clear benefit for growth rates up to 18 months of age with a post-discharge formula over a normal full-term formula.[45] It has, however, been acknowledged that differences between studies with regard to methodology, inclusion criteria, intervention periods, outcome parameters, and formula compositions may confound such review data.[24] A recent systematic review concluded that, despite marked differences in study design, nutrient-enriched diets in post-discharge preterm infants had no negative effects on growth parameters or body composition, and that in many studies, growth parameters were shown to improve during the course of the study.[24] Overall, the data indicate that, when energy requirements are adequately met in preterm infants, protein fortification results in increased linear growth and lean mass,[24] and several studies have also indicated that the use of post-discharge nutrient-enriched formula with a higher protein-to-energy ratio encourages head circumference growth in preterm infants.[24,46–48]

Given the somewhat conflicting evidence, and the wide heterogeneity among studies and infant populations, an individualized approach to

post-discharge feeding is recommended.[40] This is particularly so for the smallest, extremely preterm infants. Preterm infants discharged home may need ongoing nutritional assessment of specific nutrient status (e.g. iron, vitamin, and minerals). This is because preterm infants are at increased risk for nutrient deficiencies, depending on the feeding mode and diet – including the composition and timing of introduction of the complementary food diet.[4]

Monitoring of growth following discharge may present a challenge for the physician.[19] While specialized post-discharge growth trajectories for preterm infants have not yet been defined,[24] it has been recommended that infant growth (weight, length, and head circumference) be monitored at discharge and every 2-4 weeks thereafter, and plotted against available growth curves (e.g. WHO growth curves or Fenton curves).[1,40] Overfeeding should be avoided once a steady growth velocity has been achieved.[24]

Chapter highlights

- Infants may be classified according to their size for gestational age (AGA, SGA, or LGA), according to birth weight (LBW, VLBW, or ELBW), or according to gestational age (extremely, very, moderately, or late preterm, versus term).
- More than 10% of infants worldwide are born preterm, amounting to approximately 15 million preterm births each year.
- Risk factors for preterm birth include young maternal age, poor maternal nutrition status/maternal under- or overweight, no prior pregnancies, a multiple pregnancy, a short interval between pregnancies, maternal infectious diseases, pre-eclampsia, or substance abuse.
- The survival of preterm infants worldwide has greatly improved during the past few decades, largely due to improvements in obstetric and neonatal care.
- However, surviving infants are at risk of short- and long-term adverse effects, including respiratory problems, growth faltering, and neurodevelopmental impairment.
- Preterm infants are a particularly vulnerable group because of the abbreviated gestational period; growth velocity and maturation is highest for organ, brain, lung, immune system, and metabolic development during the last trimester of pregnancy. Preterm infants miss part of this intrauterine developmental period, which have substantial short- and long-term implications.
- Proportional growth, rather than weight gain alone, is important both for short- and long-term outcomes in preterm infants. The Fenton charts are one of the most well-established sets of charts for assessing postnatal growth of preterm infants. The recently developed INTERGROWTH-21st charts, as well as the Olson charts, may provide additional tools to help monitor adequate growth longitudinally.

- Preterm infants have high and specific nutritional requirements, which must be met through individualized (par)enteral nutrition, human milk with fortification, or, if breastfeeding or donor human milk feeding is not possible, the use of a specific preterm infant formula.
- Medical associations such as ESPGHAN and the AAP, as well as international expert groups have published recommended ranges for enteral nutrient intakes for preterm infants.
- Goals of post-discharge nutrition are to promote breastfeeding, minimize and promptly address any nutrient deficits, support lean mass accretion, and achieve proportional weight and length gain, while avoiding rapid, excessive fat accumulation. Recommendations for post-discharge feeding and growth monitoring remain controversial, but a recent review of the literature has indicated that a higher protein-energy ratio may have beneficial effects on (balanced) growth.

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Chapter 5

Small-for-gestational age term infants (term SGA)

This chapter focuses primarily on singleton infants who are born at full term, although SGA may also occur in preterm infants and in twins or triplets.

Definition of term SGA

Intrauterine growth restriction (IUGR), which is usually diagnosed based on at least two fetal ultrasounds, may result in the birth of an SGA infant.[1]

A postnatal diagnosis of SGA ideally requires: [1,2]

1. accurate knowledge of the gestational age (ideally based on a first-trimester ultrasound);

2. accurate weight, crown-heel length, and head circumference measurements taken at birth; and

3. a specified cutoff point for each measurement, against reference data from a relevant population.

As mentioned in **Chapter 3**, infants with anthropometric measurements falling below the 10th percentile for their gestational age and gender are usually classified as SGA;[3,4] however, cutoff points vary. Other definitions of SGA have used the 3rd percentile as a cutoff, or less than –2 standard deviations from the mean.[1,2] Infants can be classified as SGA for weight only, SGA for length only, or SGA for both.[1,2]

SGA should be differentiated from LBW and IUGR *per se*. The term 'low birth weight' is an absolute measure of body weight at birth (<2,500 grams[5]), and does not take into account gestational age. In addition, SGA infants may not necessarily have experienced IUGR, and IUGR may not necessarily result in the birth of an SGA infant.[2] Some infants fitting the definition of SGA may simply be constitutionally small, rather than growth-restricted. In contrast, an infant

who has experienced IUGR, but is born to large parents and would otherwise have been constitutionally large, may *not* meet the standard criteria for SGA.[6]

The above definitions of SGA also do not consider fetal growth-modifying factors such as genetics, ethnicity, or parity. These factors can be statistically adjusted, to more accurately identify infants with compromised fetal growth.[1]

Symmetric vs. asymmetric SGA infants

Term SGA infants tend to have a lower percentage of body fat (particularly subcutaneous fat) compared with term AGA infants,[7] and display either symmetrical or asymmetric patterns of growth restriction.[8]

"Symmetric SGA" is characterized by weight, length, and head circumference all falling below the 10th percentile (or other cutoff). This SGA pattern is indicative of slow development throughout the pregnancy, but particularly of growth restriction during early pregnancy. Brain growth in these infants may be restricted if compensatory 'brain sparing' has failed to prevent reduced brain growth.[8] In general, the outcome of infants with symmetric SGA is poorer than those with asymmetric SGA, partially due to this restricted brain growth,[9,10] although this may depend upon the underlying cause of the SGA birth.

In contrast, **infants with "asymmetric SGA" have a birth weight below the 10th percentile (or other cutoff), but body length and head circumference are relatively spared, and brain growth has been preserved.** This SGA pattern is characteristic of infants who grew normally during the first two trimesters but experienced growth restriction (but brain sparing) during the third trimester.[8] Although brain sparing suggests that the structure of the brain would be normal, recent studies show an increased incidence of

microstructural abnormalities of the brain in these infants compared with AGA infants,[11] and an increased risk of neurodevelopmental problems in SGA infants showing evidence of brain sparing, compared with AGA infants or SGA infants showing no brain sparing.[11,12]

Prevalence of term SGA births

The incidence of term SGA births varies between different countries. Approximate incidences are 7%–8% in the United States[6,13,14] 6% in the United Kingdom,[6] and 10% in Australasia.[15,16]

However, the burden of SGA births is much greater in low-to-middle income countries.[17] A recent large worldwide survey estimated that 32.4 million infants were born SGA in low- and middle-income countries in 2010, constituting 27% of live births. Of these, approximately **29.6 million were born SGA at term**.[17] Two-thirds of the SGA infants were born in Asia and sub-Saharan Africa, with the majority born in India, Pakistan, Bangladesh, and Nigeria.[17] The prevalence of term SGA live births ranged between 5% in East Asia to 42% in South Asia.[4,17] Other estimates include approximately 15% in Brazil, 20-25% in the Philippines, and 13-14% in South Africa.[18]

Risk factors/causes of term SGA

Although some infants born SGA are small because of family or ethnic predisposition, many have experienced restricted growth during gestation.[4] It is often difficult to differentiate between SGA due to genetic predisposition and SGA due to other causes, but it is SGA infants who have experienced IUGR who are of medical concern.[2] Factors associated with fetal growth restriction were previously discussed in **Chapter 2**.

Specific causes of *symmetrical* SGA may include chromosomal abnormalities, constitutionally small size (e.g. due to small maternal size), early placental insufficiency, or intrauterine infection. *Asymmetric* SGA is more likely to occur because of interference with placental

function or maternal health during the third trimester.[8] These and other possible causes are summarized in **Table 8**.

Notably, maternal diet and nutritional status before and during pregnancy are important for fetal growth and development.[19] Two large observational studies have found that healthy dietary patterns are associated with a reduced risk of SGA birth.[19,20]

Table 8. Currently known factors associated with SGA birth*

Constitutional	• Genetic predisposition[2,8] • Ethnicity[8]
Fetal	• Chromosomal abnormalities (e.g. Trisomy 21)[2,8] • Congenital anomalies (e.g. heart defects)[6,8] • Chronic congenital infection (e.g. cytomegalovirus, rubella, syphilis)[8] • Multiple pregnancy[8]
Maternal	• Young maternal age[24] • First pregnancy[6,25,26] • Pre-pregnancy underweight[6,27,28] • Short maternal stature[2,6] • Smoking[6,25,28] • Pregnancy-induced hypertension[6,8] • Chronic hypoxemia[8] • Under- or malnutrition due to limited food supply or severe hyperemesis[6,8,24] • Poor dietary patterns[19,20] • Short pregnancy interval (resulting in nutrient depletion)[24] • Chronic illness[8] • Infections (e.g. malaria)[6] • Narcotics, alcohol[8,28] • Mother born as an SGA infant[1]
Placental	• Decreased placental weight/surface area[8] • Placental infarction[8] • Tumor (chorioangioma; hydatiform mole)[8] • Placental separation[8] • Twin-to-twin transfusion syndrome[8]

*Strength of evidence may differ between the factors listed.

The requirement for micronutrients increases with the demands of pregnancy,[21] but there is currently only weak evidence to support the routine use of maternal dietary omega-3 fatty acid, iron, zinc, calcium, folate, or vitamin D supplementation with regard to prevention of SGA birth.[22,23] However, micronutrient deficiencies are more common in low and middle-income countries, and a recent, large Cochrane review of studies conducted primarily in low- and middle-income countries has demonstrated a significantly lower risk of SGA births and low birth weight infants among women who received multiple micronutrient supplements that included iron and folic acid.[21]

Consequences and potential health risks in the SGA population

Various short- and long-term outcomes have been associated with being born SGA, some being more particularly related to rapid catch-up growth in infancy. These are summarized in **Figure 13,** and discussed below.

Short-term health challenges (childhood)

Infants born SGA at term are at increased risk of perinatal morbidity and mortality, depending on the degree of IUGR experienced,[1] but in general the risks are lower than those for preterm (SGA) infants.[29]

Approximately 10% of children born SGA continue to show persistent growth deficits throughout infancy and childhood.[2]

Most importantly, SGA infants are at increased risk of childhood neurodevelopmental impairment (for example, resulting in lower cognitive abilities in mathematics and reading comprehension) and childhood behavioral problems (emotional, conduct, and attention disorders).[1,3,30,31] Some data indicate that the poorest neurodevelopmental outcomes in infants born SGA may be observed among those

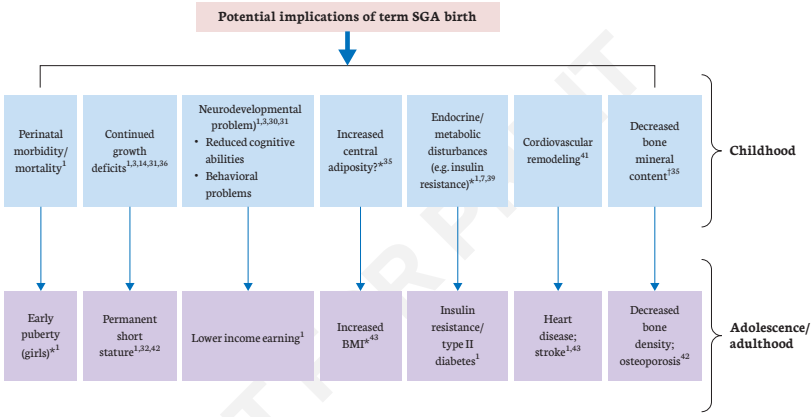

Figure 13. Potential implications of term SGA birth in childhood and beyond

Strength of evidence may differ between the outcomes listed.

**Particularly associated with rapid catch-up growth in infancy.*

†In proportion to body size. Significant association after adjustment for age, sex, and weight, but non-significant after further adjustment for height.

who fail to achieve appropriate catch-up growth in height and/or head circumference,[1,32] but the data are limited and not conclusive.[33] Early evaluation of neurodevelopmental progress is warranted in at-risk children.[1]

Data on the effects of SGA birth on body fat deposition in childhood are conflicting. A large, recent study in Eastern European children aged 6 years showed that those born SGA were shorter with a significantly lower BMI and total body fat percentage compared with those born AGA; these differences were even more pronounced at 11 years of age. However, children born SGA who showed catch-up growth during the first 3-6 months after birth had growth and adiposity measures closer to those of AGA infants.[34] Another study demonstrated overall *higher* body fat levels and central adiposity among children aged 6-10 years who were born SGA versus AGA.[35] Evidence suggests that this may be the case particularly among those who display rapid catch-up growth,[26,36–38] especially within the first 4–6 weeks after birth.[37,38]

Endocrine and metabolic disturbances (e.g. insulin resistance) in children born SGA have also been acknowledged,[1,7,39,40] particularly in those who underwent rapid postnatal weight gain.[1,7,40] There is also some direct evidence implicating SGA birth in cardiac remodeling during childhood.[41] Furthermore, some data suggest lower bone mineral contents among children born SGA compared with those born AGA.[35]

Long-term health challenges (adolescence/adulthood)

SGA infants are at increased risk of permanent short stature,[2] with average adult heights approximately 1 standard deviation below the mean population height.[1] It is thought that approximately 10%-20% reach an ultimate height below their genetic potential.[32,42]

Girls born SGA who show rapid catch-up growth during early childhood are more likely to reach puberty prematurely.[1,2,40] Also, girls born SGA are more likely to subsequently give birth to a SGA infant themselves.[1]

As mentioned in **Chapter 2**, low birth weight (including being born SGA) may be associated with an increased risk of a range of disorders in adulthood, including obesity, metabolic alterations, insulin resistance/type II diabetes, coronary artery disease, and stroke,[1,2,43] particularly among individuals who displayed more rapid catch-up growth during the first few months following birth.[2,33,44] Consistent with the lower bone mineral contents observed in some studies among children born SGA,[35] adults born SGA may be at higher risk of low bone density and osteoporosis.[42]

However, a consensus statement from various international societies of pediatric endocrinology and the Growth Hormone Research Society (GRS) states that, while these risks are present on a population level, there is inadequate evidence to recommend routine health surveillance of adults born SGA, outside of routine clinical practice.[1]

One study of long-term outcomes for term SGA individuals showed no difference in employment rates, marital status, or quality of life compared with individuals born AGA; however, those born SGA held fewer professional/managerial positions and had significantly lower incomes.[1]

Factors influencing postnatal catch-up growth in term SGA infants

Approximately 90% of infants born SGA display some degree of postnatal catch-up growth.[2] Catch-up growth, particularly early catch-up, is more likely in term SGA infants than in preterm SGA infants.[45]

The mechanisms influencing catch-up growth are not well understood,[2] but whether an SGA infant eventually achieves normal-range anthropometric measurements may depend on various factors, including:

- Birth weight[31]
- Ethnicity[31]
- Genetic and epigenetic factors[1,26]
- Prior intrauterine growth patterns[46] (onset of growth restriction in late gestation, and less severe fetal growth restriction, improve chances of postnatal catch-up growth[45])
- Intrinsic growth defects (e.g. chromosomal or congenital abnormalities)[45]
- Postnatal feeding methods[31]
- Postnatal nutrient intakes[2,26]

Cord blood leptin may also be a marker for the potential for catch-up growth. Low concentrations of cord blood leptin at birth appear to provide a signal to stimulate catch-up growth.[26,46]

There is conflicting evidence as to whether circulating levels of growth hormone and insulin-like growth factors predict subsequent growth velocity.[1,2,7]

Assessing growth differences for term SGA infants

Clinically significant catch-up growth is usually defined as a weight or length gain of greater than 0.67 standard deviation score during the first 2 years of age.[2,26,36]

Typically, a term SGA infant experiences a period of accelerated growth over the first 1-2 years,[2,26] but particularly within the first

3-6 months.[32] Catch-up growth usually begins with an increased rate of subcutaneous fat deposition.[7] Height, weight, and head circumference catch-up may not occur at identical rates.[32]

The international consensus statement mentioned above from the societies of pediatric endocrinology and the GRS recommends continued surveillance of children born SGA at term who have not achieved appropriate catch-up growth. Length, weight, and head circumference measurements are recommended every 3 months for the first year, and every 6 months thereafter.[1] If a child remains of short stature by 2 years of age, other conditions that could limit growth should be identified and managed.[1]

> . . . continued surveillance of children born SGA who have not achieved appropriate catch-up growth is recommended; length, weight, and head circumference measurements should be taken every 3 months for the first year, and every 6 months thereafter.

"Optimal" growth trajectories

Both poor and excessive infant catch-up growth patterns are associated with adverse short- and long-term outcomes. Poor catch-up growth is associated with an increased risk of childhood growth restriction, neurodevelopmental delay and impairment, and risk of infection, while excessive catch-up is associated with increased risk for childhood overweight/obesity, elevated blood pressure, and insulin resistance.[21,31,47]

Defining an optimal pattern of postnatal weight gain (linear growth and fat deposition) is therefore challenging. A balance must be achieved between the possible short-term benefits of good growth velocity for proper neurodevelopment, and the well-established

long-term risks of excessive weight gain velocity.[31,33] This issue is further complicated by current evidence suggesting that the appropriate balance may be *different* for term AGA, term SGA, and preterm infants.[33]

> Defining an optimal pattern of postnatal growth . . . is challenging. A balance must be achieved between the possible short-term benefits of good growth velocity for proper neurodevelopment, and the well-established long-term risks of excessive weight gain velocity [with regard to obesity and cardio-metabolic diseases].

One large, recently published, multicenter US study grouped term SGA infants based on different postnatal weight growth trajectories (curves), and evaluated the outcomes of each of these trajectories at the age of 7 years. Based on any increased risks of adverse outcomes during the 7 years compared with AGA infants, an "optimal" weight-to-length growth trajectory for children term SGA was established.[31] The data suggested that catch-up growth to approximately the 30th percentile in the first months, followed by more modest catch-up growth thereafter, and maintenance around the 50th percentile by the age of 7 years, may be an appropriate catch-up growth pattern which minimizes the risk of adverse outcomes.[31] While this study was newly published, it was based on infants born between the 1950s and 1970s, and newer data presents a slightly contrasting view.

A study in a more recent data set published by a well established research group in the field of infant growth,[48] has suggested that rapid weight gain (>0.5 standard deviation scores) in the first 3 months after birth is associated with a poorer cardio-metabolic health profile in adulthood (**Table 9**). It was noted, however, that neonatal weight gain

Table 9. Possible consequences of different weight growth trajectories in children born SGA at term[31,48]

Term SGA weight growth trajectory	Risks compared with AGA infants
No catch-up	Increased risk of infection in infancy, childhood growth restriction, reduced adult height, and low IQ at 7 years
Regression after 4 months	Higher risk of growth restriction
Slow catch-up	Increased risk of low IQ at 7 years*
Appropriate catch-up	Lower risk of overweight/obesity and growth restriction at 7 years; no increased risk of other adverse outcomes
Rapid/excessive weight growth catch-up	Higher risk of overweight/obesity Elevated blood pressure Reduced insulin sensitivity Unfavorable lipid profile Increased risk of cardiovascular/metabolic disease in adulthood

*Infant head circumference in particular, appears to be positively associated with neurodevelopment .[49] Note that the evidence suggesting that nutritional interventions to promote catch-up growth are associated with neurodevelopmental benefits is inconclusive. [50]
AGA, appropriate for gestational age; IQ, intelligence quotient; SGA, small for gestational age.
Adapted from Lei X, et al. *J Pediatr* 2015;166:54-8; and Kerkhof GF, et al. *A. C. S. Nat. Rev. Endocrinol.* 2012;8:689-692.

above this threshold is not necessarily 'unhealthy' if the rate of weight gain is in proportion with length gain. It is therefore important to monitor both weight and length in all infants.[48]

Nutritional management to ensure optimal growth

Dietary intervention has been shown to influence the postnatal growth trajectory in term SGA infants.[51] However, there are currently no specific nutritional guidelines for this infant population. Any available recommendations are usually based on evidence for either the mixed LBW population or preterm infants.

In current clinical practice in several countries, it is believed that in preterm infants, the benefits of catch-up growth for survival and brain development outweigh the potential long-term disadvantages related to the metabolic syndrome; but that, in term SGA infants, there is a lack of conclusive evidence that the risk of impaired brain growth (neurodevelopment) is improved by promoting catch-up growth.[50] Therefore, in term SGA infants, it is thought that active promotion of catch-up growth may not fully outweigh the long-term disadvantages with regard to metabolic risk.

Thus, given the differences in developmental stage and risks between these two groups, it is not appropriate to apply preterm feeding recommendations to term SGA infants. Further research is needed regarding the specific nutritional needs of SGA infants, and the implications of supporting adequate growth via nutritional interventions with regard to short- and long-term outcomes.

Benefits of breastfeeding

Linear growth

Some evidence suggests that breastfeeding is associated with greater body length gain at 6 months compared with standard formula feeding,[52] but other data show no greater length gains with breast- versus formula feeding.[51] The implications of breastfeeding for long-term height attainment are unclear.

Obesity and cardiovascular/metabolic risk

Breastfeeding is thought to protect healthy term infants against obesity in later life.[1,53] Whether this is true for term SGA infants has not been well established,[1,53] but breastfed term SGA infants tend to maintain more normalized rates of fat deposition and markers of insulin sensitivity and metabolic risk at 4 and 12 months compared with their formula-fed counterparts – particularly if the formula is protein-, fat-, and energy-enriched.[53]

Recent evidence also suggests a beneficial effect of breastfeeding for >6 months on cardiac remodeling of prenatal origin, in both term and preterm SGA children.[41]

Promotion of faster weight gain through the use of a nutrient-enriched (high-protein and/or high-fat) formula in term SGA infants has been shown to be associated with increased blood pressure and fat mass at the age of 6-8 years compared with standard formula feeding,[47,54] which may have implications for the development of cardiovascular disease in later life.[47,53]

In light of these long-term risks, it is thought that calorie-dense overfeeding of SGA infants is not appropriate.[1] The same principle may apply for the complementary feeding period, although specific intervention studies are lacking.

Head growth and neurodevelopment

The probable association between head growth and neurodevelopmental outcomes has been described previously in **Chapter 4**.[1,32,52] Breastfeeding of term SGA infants (with non-fortified maternal milk) has been associated with greater head circumference catch-up growth at 3 months of age,[52] and higher neurodevelopmental scores at 18 months,[50] compared with standard formula-feeding. Increasing evidence also suggests that long-term breastfeeding (≥24 weeks) may help prevent neurodevelopmental impairment in SGA infants.[1]

One study showed that faster head circumference growth was promoted with fortified infant formula compared with standard formula or breastfeeding, but it remains unclear whether this more rapid catch-up head growth is beneficial or detrimental in the long term.[51] There was no beneficial effect on developmental scores at 18 months with the enriched formula; breastfed infants achieved higher scores.[50]

Taken together, the evidence suggests that breastfeeding, which promotes a slightly slower pattern of catch-up growth (including head circumference growth) compared with formula feeding in early life may be the most beneficial approach for optimal neurodevelopment as well as minimizing long-term metabolic risks.

Other interventions

Growth hormone treatment may be administered in cases of severe growth restriction.[1,2] However, there are currently no long-term surveillance data in adults who received growth hormone during childhood for short stature secondary to SGA.[1]

Chapter highlights

- Infants are usually classified as SGA if their anthropometric measurements fall below the 10th percentile for their gestational age.
- Term SGA infants tend to have a lower percentage of body fat (particularly subcutaneous fat) compared with term AGA infants.
- Incidences of SGA vary between countries. In high-income countries, approximately 6%–10% of infants are term SGA, while the incidences are much higher in low- and middle-income countries.
- Risk factors for giving birth to a term SGA infant include genetic predisposition, fetal abnormalities, placental dysfunction, or maternal factors such as young age, underweight, first pregnancy or short interval between pregnancies, smoking and substance abuse, infections, or under-/malnutrition.
- Being born SGA may be associated with an increased risk of perinatal morbidity/mortality, and childhood neurodevelopmental disorders, continued growth deficits, and cardiac remodeling. Children who displayed rapid postnatal growth are also more likely to show higher central adiposity, endocrine/metabolic disturbances, and higher blood pressure.
- Implications of SGA birth in adulthood may include permanent short stature, as well as obesity, insulin resistance/type II diabetes, heart disease, and stroke, particularly in those who experienced rapid postnatal growth.
- Catch-up growth in SGA infants may be programmed by genetic factors, intrinsic growth defects, prior intrauterine growth patterns, or leptin signaling. Postnatal factors include feeding methods and nutrient intakes.
- The optimal growth trajectory in infants born SGA has not been definitively established, but a balance must be achieved between the possible short-term benefits of growth velocity for proper neurodevelopment, and the well-established long-term risks of excessive weight gain with regard to obesity and cardiometabolic diseases.

- Continued surveillance of children born SGA who have not achieved adequate catch-up growth is recommended.
- There are currently no specific nutritional guidelines for term SGA infants. However, there appear to be clear benefits from breastfeeding, including an optimal rate of head circumference growth (which may reflect neurodevelopmental benefits), normalized fat deposition rates, and insulin sensitivity. Given the putative long-term risks of too-rapid catch-up growth in term SGA infants, faster growth should not be promoted with a nutrient-energy enriched formula.

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Chapter 6

Large-for-gestational age (LGA) infants

Definitions of LGA and macrosomia

There is no global consensus on the definition of large size at birth in infants born at term.[1] Achieving agreement on a definition has been challenging because, like SGA infants, large neonates are a heterogeneous group in terms of ethnicity, body composition and outcomes.[2] An infant may fit the criteria for classification as LGA or macrosomic, but may simply be constitutionally large due to genetics or ethnicity. Likewise, an infant who would normally be constitutionally small may have experienced inappropriately rapid fetal growth due to a suboptimal fetal environment, but remain below the criteria for classification as LGA or macrosomic.

Macrosomia, literally meaning 'big body', is defined by the American College of Obstetricians and Gynecologists as an absolute birth weight of ≥4,500 grams.[3] The vast majority of studies, however, use a cutoff of ≥4,000 grams, but cutoffs of ≥4,100, ≥4,200, or even ≥5,000 grams have also been used in the literature.[2,4] Although an absolute weight measurement can be appropriate for certain homogeneous populations, this does not take into account the important impact of gestational age on birth weight.[5]

Increasingly, therefore, growth chart cutoffs such as the 90th percentile, or 2 standard deviations above the mean weight of infants of the same sex and gestational age for a particular population, are being used to classify infants born LGA.[1,2,5] Occasionally, the 95th or 97th percentile has also been used as a cutoff point.[1]

Prevalence of LGA/macrosomia

Given the lack of consistent definitions, the exact prevalence is difficult to establish. In high income countries, national prevalence of macrosomia is reported to be between 5% and 20%,[2,5,6] with the highest prevalence found in the Nordic countries[2,6] (**Table 10**). Increases in prevalence of up to 25% have been observed over the past two to three decades, in parallel with increases in maternal obesity and diabetes, and substantial reductions in maternal smoking.[2,5]

Table 10. National prevalence studies of high birth weight, termed "macrosomia" or "LGA", in singleton pregnancies

MACROSOMIA: Absolute birth weight		
Country	**Data collection period**	**Estimated prevalence**
Cutoff: ≥4000 g		
USA[10]	1994-1996	14%
Canada[11]	1995-1996	14%*
Latin America[5]	2004-2005	3%-9%
Australia[12]	1988-2005	13%
Europe		
Denmark[6]	1990-1999	20%
Belgium[13]	2010	9%
Asia		
China[5,14]	2007-2008	7%-8%
China[15-20]	2010-2012	7%-14%
Hong Kong[21]	1995-2009	3%
Taiwan[22,23]	2008-2010	2%
Japan[24-27]	1990-2013	1%-6%
South Korea[28,29]	2005-2010	3%
Malaysia[30]	1989	3%
Low-to-middle income Asian countries (e.g. Sri Lanka, Nepal, Vietnam, Cambodia, Thailand, Philippines)[5]	2007-2008	1%-7%
Low-to-middle income African countries[5]	2004-2005	2%-15%
Cutoff: ≥4500 g		
Canada[11]	1995-1996	2%*
Australia[31,32]	1991-1994; 2002-2004	2%
Sweden[33]	1992-2001	5%
Africa (Nigeria)[34]	1999-2003	3%

Table 10. (continued)

LGA (birthweight according to gestational age†)		
Country	**Data collection period**	**Estimated prevalence**
Cutoff: >90th percentile		
USA[7,35]	1997-2005	9%-12%
Canada[36]	1994-1996	12%
Asia		
China[14]	2000-2005	18%
Hong Kong[37]	1995-2005	9%
Japan[24]	2008-2010	16%
South Korea[29,38]	2005-2010	8%
Vietnam[39,40]	2007-2011	10%-12%
Thailand[41]	2011-2012	7%
Indonesia[42,43]	2001-2004	9%-10%
India[44,45]	2009-2012	10%-12%
Bangladesh[42,43]	2001-2004	11%
Pakistan[42,43]	2002-2004	8%
Nepal[42,43]	2002-2004	8%

*Non-native Canadian population

†Growth reference standards vary between studies

Interestingly, however, slight decreases of up to 2% in the incidence of LGA birth have recently been reported in the USA and Denmark.[7-9] The postulated explanation in the Danish cohort was a simultaneous increase in early term deliveries due to induced labor and elective cesarean sections;[9] but this was not the case in the US cohorts, where the decline in LGA birth was evident at every gestational age, and even when overall gestation length did not change.[7,8]

In low-to-middle income countries, the prevalence of macrosomia varies considerably; African data range between 2%-15%, Asian data from 1%-7%, and Latin American data from 3%-9%.[5] Rates in low- and middle-income nations appear to be increasing at a slower rate than in high-income countries.[5]

Risk factors for LGA

Maternal diabetes is one of the strongest risk factors associated with giving birth to a large-sized infant.[4,46–49] Maternal hyperglycemia leads to fetal hyperglycemia, which stimulates the fetal pancreas to produce and secrete more insulin – ultimately resulting in fetal hyperinsulinemia.[46] Fetal hyperinsulinemia promotes body growth, and specifically the development of (excessive) adipose tissue mass. Thus, large infants born to diabetic mothers may show increased neonatal adiposity compared with large infants born to non-diabetic mothers.[48]

> Key risk factors for LGA birth include pre-pregnancy obesity, excessive gestational weight gain, and gestational diabetes.

Maternal overweight or obesity prior to pregnancy also increases the likelihood of giving birth to an LGA or macrosomic infant[1,46,50] with higher neonatal adiposity, particularly central adiposity.[51,52] A strong association, independent from pre-pregnancy weight, has also been demonstrated between excessive maternal gestational weight gain and LGA birth,[46,49,53] However, the *combination* of maternal obesity and excessive gestational weight gain dramatically increases the absolute risk of giving birth to an LGA infant.[46,49] Gestational diabetes may occur secondary to overweight and excessive maternal gestational weight gain,[46,47] and even further increases the risk of LGA birth.[4,46–49]

Besides obesity, weight gain, and diabetes, several other factors that may contribute to the risk of macrosomic/LGA birth are listed in **Table 11,** although it should be noted that there is substantial variation in the literature as to the strength of these associations.[4] In fact, most at-risk pregnancies will not result in a macrosomic infant, and therefore interventions to reduce the burden of adverse outcomes associated with macrosomia are controversial.[4,54]

Table 11. Risk factors for LGA birth and/or macrosomia

Fetal factors	• Male sex*[4,5,31,55] • Post-term delivery (>40-42 weeks' gestation) [4,5,31,55]
Maternal factors	• High pre-pregnancy BMI[1,4,5,31,50,53] • Excessive gestational weight gain (e.g. >18 kg for women with normal pre-pregnancy BMI†)[4,53,56] • Hyperglycemia[53]/gestational diabetes[4,5,48,55] • Hypertension[4] • Tallness[5,53] • Smoking cessation during pregnancy[4] • Older age[4,5,55] • Previous macrosomic birth[4] • Increasing birth order/high parity[1,5,55] • Longer inter-pregnancy interval[4] • Antidepressant use[53] • Parental birth weights[4] • Genetic polymorphisms e.g. *737.738 IGF1* polymorphism (possibly linked to higher fetal IGF-I levels) [57]

**When same absolute cut-off is used for both sexes.*

†Classification of "excessive" gestational weight gain is dependent upon pre-pregnancy BMI, and the guidelines differ. Institute of Medicine (IOM) guidelines[56] suggest a gestational weight gain of 11.5–16 kg (0.42 kg/week) over the duration of pregnancy for women of a normal pre-pregnancy BMI (18.5–24.9 kg/m^2). Lower total weight gain is recommended for women of high pre-pregnancy BMI, while higher total weight gain is recommended for women who were underweight before conception.

Consequences

Neonatal health

Macrosomic infants are at an increased risk of labor and delivery complications, birth by cesarean section, birth injuries, and neonatal morbidity and mortality; these risks increase in parallel with increases in birth weight.[4,5,55] Macrosomia is also associated with an increased risk of adverse maternal outcomes including uterine atony, prolonged labor, abnormal postpartum hemorrhage, severe perineal lacerations, infection, and thromboembolic events;[1,4,5,55] hence the recent focus to manage large-for-date fetuses through induction of labor where appropriate, rather than with expectant management.[4]

Neonates undergo a process of metabolic adaptation after birth, after an abrupt stop to the continuous placental glucose supply and a subsequent transition to intermittent enteral feeding.[58] Thus, in the first few hours after birth, blood glucose levels normally decline, followed by a brisk ketogenic response.[58] Early hypoglycemia is frequently diagnosed in LGA infants,[10,59] probably as a result of hyperinsulinemia, and thus routine glucose testing is indicated.[59] LGA infants born to diabetic mothers are particularly prone to hypoglycemia after birth.[10,58,60] The literature indicates that approximately 30% of macrosomic infants from diabetic mothers, compared with approximately 9% of LGA infants from non-diabetic mothers, experience at least one episode of hypoglycemia during the first hour after birth.[10,59] Most infants respond rapidly to early breast- or formula feeding, or intravenous glucose supplementation in more severe cases.[10] Research is currently underway to investigate whether antenatal breastmilk expression in women with diabetes helps promote more rapid milk production after delivery.[61]

At birth, LGA neonates show significantly higher *absolute* amounts of both total body fat and lean body mass compared with AGA neonates, but tend to also have a higher proportion of total body fat in relation to lean body mass, as a percentage of body weight.[48,62,63] In addition, LGA infants from mothers with gestational diabetes show particular patterns of adiposity (in particular increased central adiposity) compared with other LGA infants.[48]

> In macrosomic infants, the risk of labor complications, birth injuries, and neonatal morbidity and mortality increase in parallel with increases in birth weight. Macrosomia is also associated with an increased chance of cesarean section . . . and adverse maternal outcomes including uterine atony, prolonged labor, abnormal postpartum hemorrhage, severe perineal lacerations, infection, and thromboembolic events.

Infant growth and development

After escaping the strong maternal influence on growth *in utero*, following birth the neonate begins to default to its genetically determined growth trajectory.[64] This results in a wide variation in linear growth and weight gain patterns during early infancy.[64]

Many children born LGA show a measure of catch-down (decelerated) growth in the first year, particularly in the first few months;[1,65] by 6-12 months of age, this tends to result in substantial realignment of all growth parameters compared with infants born AGA.[1]

However, one study has indicated that infants born LGA are 4.6 and 2.2 times more likely to remain overweight at 6 and 12 months of age, respectively, compared with AGA infants,[66] and another study reported that mean body weight of children born LGA remained around the 70th percentile through 4 years of age.[63] Further study is required to establish the reasons for these differences in postnatal growth trajectories in different LGA infant populations.

It is therefore difficult to accurately define appropriate postnatal growth trajectories for infants born LGA.[1] It is important to consider not only birth status but also parental characteristics and genetic constitution when using postnatal growth charts for LGA infants. As with SGA and preterm infants (discussed previously), ongoing growth monitoring is very important, particularly to ensure proportional weight-for-length growth.

> The growth of LGA infants should be considered relative to their birth status when using postnatal growth charts. Ongoing growth monitoring is very important particularly to ensure proportional weight-for-length growth.

Development through to adulthood

Individuals born LGA tend to remain taller and heavier up to adulthood compared with their AGA counterparts.[57] The positive association between LGA birth and childhood BMI/obesity also tends to persist through adolescence and into adulthood, particularly when no catch-down growth occurred during infancy and childhood.[1,46,57,67-69] Specifically, epidemiological studies have shown a 30-50% increased risk of overweight during adolescence with every 1 kg increase in birth weight.[46] However, more detailed data are needed to establish the effect of birth weight on body composition, as both excessive fat mass and increased lean mass deposition may underlie later differences in BMI.[70,71]

This positive association between birthweight and long-term overweight risk is independent of ethnic/geographic differences, gender, socioeconomic status, or maternal body weight,[68] and may be related to increased fat accumulation[1,46,72,73] – particularly in children who continued to show rapid growth, with no catch-down growth period, in the first two years after birth.[46,74] The result may be an overweight adult who, if female, is at risk of giving birth to her own LGA infant, creating a perpetual cycle – particularly if she gains weight excessively during her pregnancy (**Figure 14**).[46,60] Fortunately, both pre-pregnancy weight and gestational weight gain are modifiable factors, at least to some extent,[53] and are thus clinically important considerations from a public health perspective.[46]

In addition, several studies suggest that LGA birth is strongly associated with adverse metabolic outcomes in childhood, including insulin resistance, high blood pressure, and dyslipidemia, particularly among children born to mothers with obesity and/or gestational diabetes.[1,75,76]

Although in most studies increasing size at birth has been associated with a *decreased* risk of type II diabetes in adulthood,[51,77] other studies (particularly in populations with high prevalence of maternal

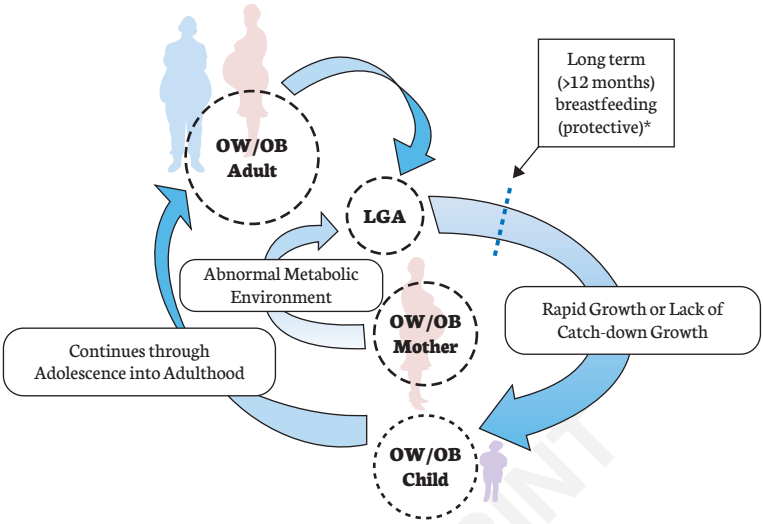

Figure 14. Perpetual cycle of obesity through accelerated growth velocity without intervention

Adapted from Adamo KB, et al. *Int J Environ Res Public Health* 2012;9:1263-1307.

*See Camurdan MO, et al. *J Pediatr Endocrinol Metab* 2011; 24(7-8):463-8. OB, obese; OW, overweight; LGA, large-for-gestational-age.

diabetes) have shown an *increased* risk.[1,51,77,78] There also appears to be a continuation of the increased risk of high blood pressure[57] and the metabolic syndrome[76] into adulthood in individuals born LGA, as well as a higher risk of heart disease.[76] As shown in **Table 8**, the *737.738 IGF1* polymorphism has been implicated in large birth size, and it is thought that this polymorphism may also play a role in LGA-associated cardio-metabolic outcomes (such as type 2 diabetes and cardiovascular disease) through enhanced expression of the *IGF1* gene, which is related to the increased secretion and action of insulin and insulin-like growth factors.[57]

Furthermore, LGA status at birth has been associated with a greater risk for several cancers – best documented for breast cancer in females born LGA.[67,78]

The impact of nutrition

Benefits of breastfeeding

Breastfeeding is considered the most safe, practicable, and desirable method of ensuring successful metabolic adaptation after birth.[58] While the literature on nutritional management of LGA infants is scant, evidence suggests that breastfeeding, and specifically a long duration breastfeeding (>6-12 months) may help to realign to normal growth patterns.[65,79]

In one Turkish study,[65] exclusively breastfed infants born AGA or LGA achieved comparable BMI values at 4 months of age. Prolonged breastfeeding (>12 months) also resulted in similar BMI values in AGA and LGA infants, whereas LGA infants who discontinued breastfeeding earlier (<12 months) maintained a higher mean BMI during the first 3 years compared with children born AGA.[65] There may be potential for confounding in this study, as breastfeeding for >12 months is likely to be associated with other lifestyle and dietary patterns that could affect BMI.

An American study also showed that breastfeeding for at least 6 months helped to protect against subsequent extremes in body size and fat deposition in children aged 6-13 years.[79]

The current prevailing hypothesis is that prolonged breastfeeding may encourage proper self-regulation of energy intake and avoidance of overfeeding. It has been suggested that breast milk leptin signaling of growth, appetite, and nutrition regulation may in part explain this association.[80] In non-breastfed infants, parents should be cautious not to force-feed or over-feed, but also not to underfeed with the intention of avoiding further weight gain. Interestingly, one observational study showed that stricter dietary restraint by the mother in early life was associated with a higher risk of child overweight at 12 years of age.[81]

Currently, it is generally agreed that, for formula-fed LGA infants, intakes should resemble those for AGA infants. This approach may also be relevant during the weaning period when solid foods are introduced, and after throughout the toddler period when it remains important not to under- or over-feed a child, in order to develop healthy eating habits and encourage appropriate satiety signaling. Clearly, more research is needed to understand the role of feeding type and feeding habits during the entire infant/toddler period, in relation to the risk of overweight in LGA offspring.

Identification and monitoring

As discussed in **Chapters 2** and **3**, it is important to monitor growth during both the fetal and neonatal periods.

As part of proper antenatal care, ongoing prenatal growth surveillance using appropriate reference charts (e.g. INTERGROWTH-21st charts) helps identify fetuses who are likely to become LGA at birth. Notably, some studies have proposed the use of a lower cutoff value than the 90th percentile specifically for infants born to mothers with gestational diabetes, given the higher fetal morbidity risk in this population.[5]

Serial postnatal growth measurements plotted against an international growth standard (e.g. WHO child growth standards) help to identify infants born LGA who are not showing appropriate catch-down growth. There is currently a lack of clear guidance as to what constitutes "appropriate" postnatal growth for LGA infants, but more intensive monitoring may be warranted for LGA infants, given the known risks for subsequent childhood overweight and metabolic health.

Rather than considering fetal and postnatal growth separately, it may be more important to combine fetal and postnatal growth measures to

assess the potential for growth deviations throughout childhood. For example, in Asian women, although the risk of LGA birth is reported to be lower compared with the risk in Caucasian women, Asian women are at an increased risk of developing gestational diabetes, which is in itself a risk factor for rapid postnatal growth and later overweight, irrespective of birth weight.[37,82] Assessment of the entire growth continuum may therefore be particularly important in certain populations.

Chapter highlights

- There is no consensus definition of large size (LGA or macrosomia) at birth; thus, the exact prevalence is difficult to establish. In high income countries, the prevalence of macrosomia is approximately 5%-20%, and is increasing in most countries in parallel with increases in maternal obesity and diabetes. Macrosomia prevalence in low-to-middle income countries range from approximately 1% to 15%, and are increasing more slowly.
- Key risk factors for LGA birth include maternal obesity, excessive gestational weight gain, and gestational diabetes. Fetal factors include male sex and white race, and additional factors may include genetic influences, older maternal age, post-term delivery, multiparity, and a lengthy interval between pregnancies.
- Consequences of macrosomia may include an increased risk of:
  - Labor complications, birth injuries, cesarean section, and neonatal morbidity and mortality.
  - Continued overweight in childhood, as well as adverse metabolic outcomes, particularly among children born to obese mothers with/out gestational diabetes.
  - Persistent overweight into adulthood, as well as high blood pressure, metabolic syndrome, heart disease, and cancer. The link between macrosomia and adult type II diabetes is controversial.
- It is difficult to accurately define appropriate postnatal growth trajectories for infants born LGA, and it has been suggested that the growth of LGA infants should be considered relative to their birth status when using postnatal growth charts.
- Many children born LGA show a measure of catch-down growth in the first year, particularly in the first few months, which tends to result in substantial realignment of all growth parameters compared with infants born AGA. Overall LGA children regardless of their growth velocity may remain larger and heavier than AGA

children through at least 4 years of age, which is a risk factor for later obesity and metabolic disease.

- Evidence suggests that breastfeeding for as long as possible may help encourage realignment of normal growth parameters, probably in part by encouraging proper self-regulation of energy intake and avoiding overfeeding.

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SECTION C

Challenged growth

Chapter 7

Inadequate growth during infancy and childhood

From reduced length gain to stunting and from weight loss to wasting (thinness)

Infants and young children are among the most nutritionally vulnerable in any population, due to their physiologically higher nutrient requirements,[1] and child malnutrition is a leading cause of impaired growth velocity and failure-to-thrive.[2] However, there is evidence that earlier factors in the life continuum, including maternal nutritional status, disease, and other exposures during the periconceptional period and pregnancy, may influence later growth patterns and health outcomes.[1,3]

The global burden of malnutrition includes growth faltering, underweight, stunting, wasting (thinness), micronutrient deficiencies, and overweight. In children, these conditions can exist separately or in combination, but can also progress over time from less severe or long-lasting malnutrition to more severe, chronic states such as stunting and wasting.[4]

Globally, stunting, wasting, and micronutrient deficiencies are estimated to collectively contribute to over 3 million childhood deaths annually.[5] This chapter focuses primarily on stunting and wasting/thinness in children under the age of 5 years, which are over-represented in low- and middle-income versus high-income countries.[6]

In this chapter, we first define growth faltering, malnutrition (undernutrition), underweight, stunting, wasting (thinness), and severe acute malnutrition. We then focus on the prevalence, risk factors, impact, and clinical management of stunting; and to a lesser degree, of wasting and severe acute malnutrition. It is important to note that, given that the underlying causes of these conditions may be different between low-, middle-, and high-income countries, relevant issues and management will differ depending upon the environment.

Definitions

Growth faltering or failure-to-thrive

The terms "growth faltering" or "failure-to-thrive" are used in pediatrics to describe inadequate weight or height gain (or both), or the inability to maintain adequate weight or height growth. These conditions may occur due to a lack of nutrients, but because many physiological, psychosocial, and environmental factors can lead to undernutrition, and because there is no consensus on specific anthropometric criteria that define it, these terms should not be used as actual diagnoses.[7,8]

The terms "underweight" (low weight-for-age), "stunting" (low height-for-age), and "wasting" (low weight-for-height) are preferably used to describe and quantify the degree of infant or child malnutrition (**Figure 15**).[9-11]

Malnutrition (undernutrition)

The general term "malnutrition" actually refers to both undernutrition and overnutrition (see **Chapter 8**).[12] Malnutrition in the context of undernutrition is defined as underweight,[12] (which may reflect stunting or wasting), and may be caused by a deficiency of macro- or micronutrients.

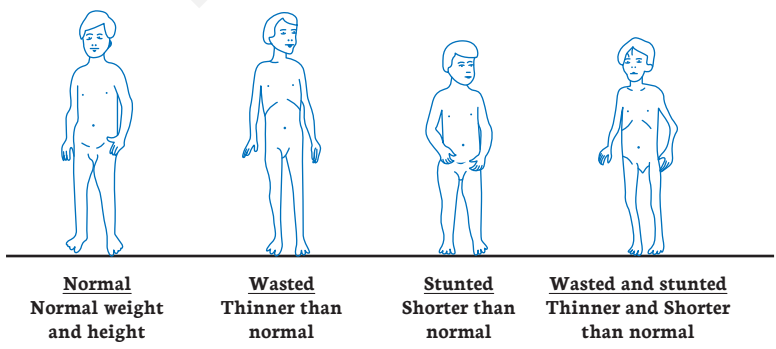

Figure 15. Representation of stunting and wasting in children of similar age

Severe acute malnutrition (SAM) – previously called marasmus – is characterized by wasting of muscle and fat tissue; at the same time edema (particularly ascites) may occur (previously referred to as kwashiorkor). A child with undernutrition can present with both these conditions simultaneously.[2]

Micronutrient malnutrition refers to chronic micronutrient intake deficits. Globally, the most frequent form of micronutrient malnutrition during the first 1000 days is iron deficiency, followed by vitamin A, folic acid and iodine deficiencies.[13]

Underweight, stunting, wasting (thinness), and severe acute malnutrition

Underweight may be a consequence of acute or chronic undernutrition and/or compromised health status.[14,15] The WHO definition of underweight is low weight-for-age, defined as greater than 2 standard deviations below the mean of the WHO international growth standards.[11,16] Underweight children can be wasted with or without stunting (**Figure 15**).

Stunting refers to severely limited linear growth, which has to be present for a period of time before the child develops stunting.[9,10] Stunting is thought to be a stronger indicator of chronic undernutrition than underweight.[14,15,17,18] There is international agreement on the definition of stunting. The WHO defines stunting as length-for-age (infants) or height-for-age (children) greater than 2 standard deviations below the mean of the 2006 WHO growth standards.[11,16,19,20]

Wasting is an indicator of acute malnutrition,[14,15] and is a term mainly used in relation to children in low- and middle-income countries. The term "thinness" is more frequently used in high-income countries. The WHO defines wasting as low weight-for-length (infants) or low weight-for-height (children), defined as greater than 2 standard deviations below the mean of the WHO growth standards.[11,16] However, some studies define wasting as low BMI-for-age.[9]

Severe wasting is an indicator of SAM, and in children aged 6–60 months, is defined by the WHO as 1) weight-for-height greater than 3 standard deviations below the mean of the WHO standards; 2) mid-upper arm circumference <115 mm (based on WHO standards); and/or 3) presence of bilateral edema.[21]

Underweight: Prevalence and timing

The global prevalence of underweight has decreased steadily, from approximately 25% in 1990, to 14% in 2014. In 2014, 16% (95 million) of children below the age of five in less developed regions of the world were underweight.[22]

Mean weight-for-age tends to start faltering at approximately 3 months of age, and declines rapidly until about 12 months, after which there is a slower decline until approximately 18 months, sometimes followed by a pattern of catch-up growth.[15,23–25]

Stunting: Prevalence, causes, timing, impact, and management

Prevalence and burden of stunting

Although stunting affects large numbers of children globally,[20,26] 80% of the world's stunted children reside in only about 20 countries,[27] with 40% residing in India.[4]

- The global prevalence and burden of stunting in under-5-year-olds is slowly decreasing; the prevalence decreased from approximately 40% in 1990 to 25% (i.e. one in four children) in 2012, with a corresponding decrease in burden from approximately 253 million to 162 million (**Table 12**).[28,29]
- In India, through national intervention efforts the rate of stunting decreased from 48% in 2006 to 39% in 2014.[4]

Table 12. Approximate global prevalence of stunting, wasting, and severe wasting in children under the age of five between 1990-2016

	Stunting	Wasting	Severe wasting
1990	40%[29] (253 million) [26]	9% (58 million) [26]	-
2011	26% (165 million) [26]	8% (52 million) [26]	3% (19 million) [26]
2016	24% (159 million) [31]	8% (50 million) [31]	-

However, the current global decline in stunting is considered to be slow, and remains uneven between countries.[4,18] In Asia, the overall prevalence of stunting more than halved between 1990 and 2015, from 49% to 23%;[29] whereas in Africa, stunting prevalence has consistently remained around 40% since the 1990s.[29] Given the population growth occurring in Africa, this translates to an increased number of stunted children and a corresponding increase in stunting burden.[29] The greatest absolute number of children affected by stunting resides in south-central Asia.[30] The prevalence of stunting remains four times as high in low-to-middle income countries (28%) compared with high-income countries (7%).[26]

For newborn stunting (defined as less than the 3rd percentile of the INTERGROWTH-21st length-for-gestational-age standards), an international cross-sectional study reported a prevalence of 3.8%.[9]

Risk factors for stunting

While stunting and wasting share several common determinants, they are two distinct phenotypes with diverging risk factors (**Figure 16**), as well as distinct timings and prognoses (discussions to follow).[9,32]

There is a broad spectrum of direct and contextual influences contributing to the risk of stunting, from preconception through gestation, infancy, and childhood.[18,20]

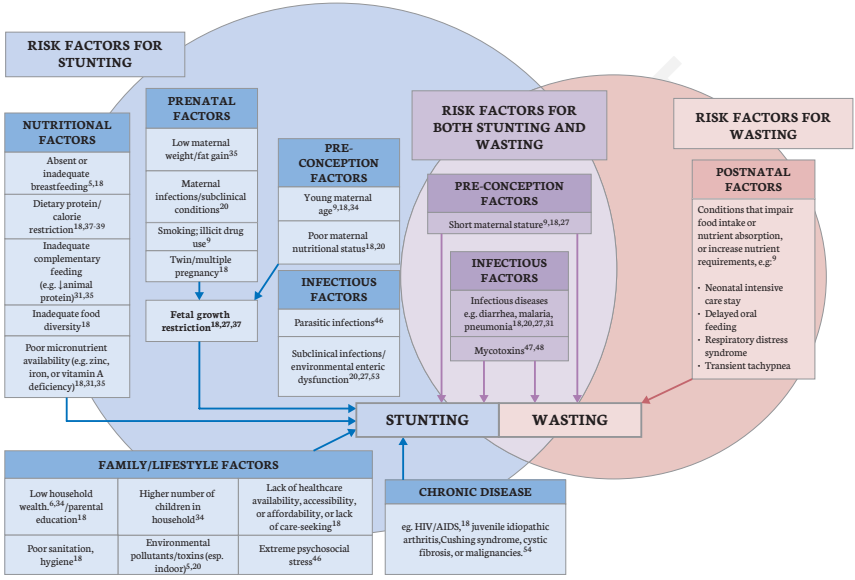

Figure 16. Probable risk factors for stunting, wasting, or both

1. Pre-conception

Short maternal height,[9,26] young maternal age,[9,33] small pre-conception maternal body size,[34] low maternal birth weight,[35] lower maternal education,[18] low household wealth,[18] and poor maternal nutritional status prior to conception[20] are thought to be important risk factors for both small infant size at birth (as previously discussed in **Chapters 2** and **4**) and early childhood stunting.

2. Prenatal factors

Fetal growth restriction, for example due to maternal malnutrition, is associated with an increased risk of stunting in early childhood.[26,36] A study conducted in Egypt and Kenya showed that low maternal weight and fat gains during pregnancy were associated with both small size at birth and stunting during the first six months.[34]

Multiple births are also associated with a risk of childhood stunting, as is a shorter interval since a preceding birth.[18]

It is known that maternal infections and subclinical conditions during pregnancy are risk factors for both intrauterine growth restriction and postnatal stunting, and studies evaluating the possible benefits of better control of maternal infection are ongoing.[20]

Other prenatal factors associated with stunting include smoking[9] and illicit drug use.[9]

3. Postnatal factors

Inadequate nutrient intake during the postnatal period

Inadequate nutrition is an important factor contributing to compromised growth.[18,32] Linear growth is mediated by both hormonal and nutritional factors which regulate the process of endochondral ossification at the growth plates of the long bones. Caloric restrictions and deficiency of macro and micro nutrients may impair the rate of longitudinal bone growth.[36–38]

Often stunting does not occur until later in infancy. Inadequate complementary feeding is a major contributor to stunting,[30] particularly if intakes of animal protein are low,[34] or when food diversity or quantity is poor.[18] An important dietary factor affecting linear growth – and thereby adult height – appears to be the ratio between intakes of high-quality proteins from dairy, meat, and fish, and low-quality proteins from grains.[39,40]

In addition, some micronutrients are essential for linear growth. For example, stunting is widely held to be a marker of zinc deficiency.[30] Zinc and iron bioavailability may be compromised in some countries with relatively high dietary intakes of phytate, fiber, and tea.[34] There is also some evidence suggesting an important role of micronutrient availability on growth hormone secretion, in particular vitamin C[41] and possibly vitamin A.[42]

Infections and other exposures

The link between infections, particularly gastrointestinal infections, and linear growth retardation is well established. Infection, including diarrhea, can cause poor nutrient absorption, nutrient losses due to diarrhea, and reduced appetite, all of which adversely affect linear growth.[20,30] Acute or chronic diarrhea appears to be the most important consequence of infectious diseases contributing to stunting;[26,30,43] each additional episode of diarrhea is thought to increase the odds of stunting by approximately 4%.[44] Other important infections include respiratory diseases (pneumonia), malaria, and measles.[26,30] Infections may also occur in combination with intestinal parasitic infestations which may cause nutrient malabsorption.[45] Furthermore, chronic dietary exposure to mycotoxins produced by molds has been implicated in growth impairment in two studies in African countries.[46,47]

Importantly, malnourished children tend to be immunodeficient, and thus more susceptible to infection,[48-50] resulting in a self-perpetuating cycle.[51]

> Subclinical environmental enteric dysfunction may be an important cause of the reduced efficacy of nutritional interventions during the complementary feeding period, and increased risk of serious infection observed among children with undernutrition in low- and middle-income countries. As part of an integrated approach to improving stunting rates, it is therefore considered important to reduce exposure to possible causes of environmental enteric dysfunction, including gut infections (e.g. *Helicobacter pylori*), micronutrient deficiencies, and environmental toxins, and to improve hygiene, water supply, sanitation, and the balance of the gut microbiota.

It is also thought that subclinical conditions, such as environmental enteric dysfunction and other physiological responses to environmental toxins or pollution, may account for a large proportion of the global stunting burden, because they are likely to be far more frequent than clinically evident infections.[20] While the mechanisms by which environmental enteric dysfunction affects linear growth are not fully clear, reduced gut barrier integrity and absorptive capacity, and mucosal inflammation, may reduce nutrient uptake.[26,52] It is believed that environmental enteric dysfunction may be an important cause of the reduced effectiveness of nutritional interventions during the complementary feeding period, and increased risk of serious infection observed among children with undernutrition in low- and middle-income countries.[52] As part of an integrated approach to improving stunting rates, it is therefore considered important to reduce exposure to possible causes of subclinical conditions, including gut infections (e.g. *Helicobacter pylori*), micronutrient deficiencies, and environmental toxins, and to improve hygiene, water supply, sanitation, and the balance of the gut microbiota.[20,26,52]

Chronic conditions

Genetic and endocrine factors, as well as chronic disease, may contribute to linear growth aberrations after birth.

Relevant causes of growth stunting in high-income countries may include genetic syndromes (e.g. Noonan syndrome or Turner syndrome), growth hormone deficiency in children over 6 months of age, or a range of pathologic states or diseases such as hypothyroidism, gluten enteropathy, juvenile idiopathic arthritis, Cushing syndrome, cystic fibrosis, or malignancies.[53]

Family/lifestyle factors

In low and middle-income countries, household wealth at birth is negatively associated with stunting risk.[6,33] Conditions of poverty and deprivation during the first 1,000 days increase the likelihood of growth faltering which could lead to stunting in later childhood, even among children whose wealth circumstances later improve.[6] A high number of children in the family is also associated with a risk of stunting;[33] this may possibly be related to short birth intervals and maternal (micro)nutrient status.

Finally, stunting may, in rare cases, reflect extreme psychosocial stress without nutritional deficits.[45]

Typical timing of stunting

Stunting (low height-for-age) and wasting (low weight-for-length) appear to have slightly different and quite characteristic timing patterns (see **Figure 17**).

Faltering of length gain appears to follow a similar timing pattern in most developing regions of the world.[36] Linear growth failure can begin as early as the second trimester of pregnancy,[36] and persist up to 2 years and beyond. Stunting cases are usually diagnosed in the later phase of the first 2 years of age.[9,24]

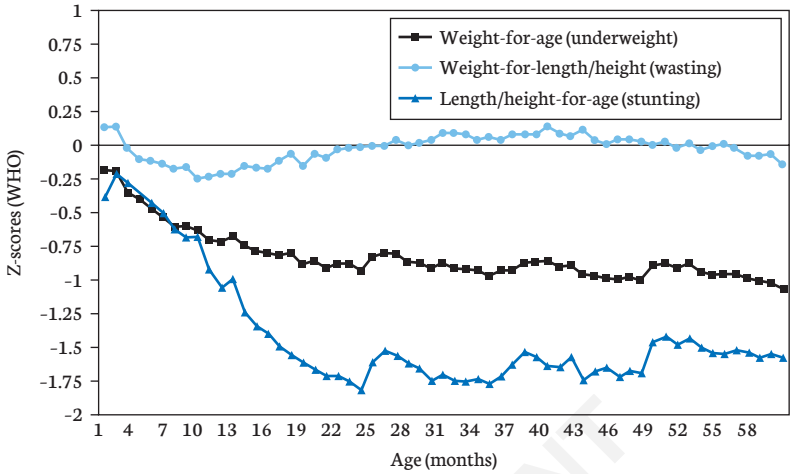

Figure 17. Mean anthropometric z-scores (number of standard deviations away from the WHO standard) by age, in low- and middle-income countries[24]

Adapted with permission from: Victora CG, et al. *Pediatrics*. 2010;125:e473–80.

Health risks and other consequences associated with stunting

Stunting in early life is associated with serious short- and long-term health risks for the infant (**Table 13**).

Stunting at birth may predict short stature in early childhood. One Indonesian study showed that length at birth was a stronger determinant of height-for-age at one year than any other factor examined,[54] while a study in Malawi estimated that approximately 20% of the 10-centimeter height deficit at the age of 3 years was already evident at birth.[55] In high-income countries, however, only about one-third of children born with fetal growth restriction remain small in stature.[36]

In low- and middle-income countries, suboptimal growth, according to anthropometric indicators of stunting, wasting, or underweight, is associated with a higher risk of mortality in the first 5 years of age,

Table 13. Health consequences associated with stunting and wasting

Stunting consequences
Short-term
Higher mortality in early childhood[5,26]
Impaired cognitive development, motor performance, and educational performance[20,26,56]
Lower height at 2 years of age[17]
Long-term
Permanent short stature[36]
Reduced income and productivity[17,20,26,29,36]
Depression, anxiety, and hyperactivity in adolescence; ADD in adults[26]
Chronic nutrition-related diseases[*†17,21,29,36]
Females: Giving birth to low birthweight infant[17,36]
Females: Early menarche[*58]

ADD, attention deficit disorder
*Particularly if rapid catch-up growth occurs[17,29]
†Only if rapid catch-up growth occurs after 2 years of age[17]

particularly with regard to death from infectious diseases such as infectious diarrhea, pneumonia, and measles.[5,26] Children with concurrent stunting, wasting, and underweight are reported to be at approximately 12 times higher risk of mortality compared with children showing no nutritional deficits.[4] In 2011, it was estimated that more than 1 million childhood deaths per year were attributable to complications due to stunting, and about 800,000 to wasting – about 60% of which were due to severe wasting.[26] Generally, the younger the child,[44] and the more severe the degree of stunting,[26] the higher is the mortality risk.

The literature strongly suggests that stunting in early life is associated with impaired cognitive and motor development and poor educational performance.[20,26,56] Some stunted children have also been found to display behavioral differences, including apathy, low mood, and reduced activity and curiosity.[26]

Long term

Growth deficits accumulated during the first 1,000 days can be very difficult to reverse or correct for later, resulting in persistent short stature.[36] Height at 2 years of age is a strong predictor of adult height.[26]

Small size at birth and short stature at 2 years of age are associated with reduced educational attainment, low adult wages, and lost economic productivity.[17,20,26,29,36] Additionally, the literature suggests an association between stunted growth at 2 years of age and an increased risk of depression, anxiety, and hyperactivity in adolescents, as well as attention deficit disorder in adults.[26]

Female children who are stunted are at risk of giving birth to low birthweight infants later in life, creating an inter-generational cycle of stunting.[17,36] In those who are stunted but experience rapid catch-up growth, there are indications of possible early menarche onset.[58]

Stunting is associated with an increased risk of nutrition-related chronic cardiovascular and metabolic diseases in later life, especially when accompanied by rapid or excessive weight gain in later childhood.[17,20,29,36] However, there does not appear to be an increased risk of such diseases in low- and middle-income countries if rapid weight or length gains occur during the first two years of age following poor fetal growth.[17]

Opportunities to prevent or reverse stunting

Stunting should be considered as a matter of serious concern, but is considered to be largely preventable and treatable. Prevention is the key goal, and timely efforts to intervene in cases of early growth deviations that may lead to stunting should be undertaken wherever possible.

As discussed in **Chapter 1**, the WHO adopted a resolution in 2012 on maternal, infant, and young child nutrition that included a global

target to reduce the number of stunted children under 5 by 40% by the year 2025.[20] These goals were based on historical national successes in tackling undernutrition. At current rates, the reduction in stunting is likely to be only 26%, although Asia as a whole is on track to achieve or surpass the WHO target.[20]

Encouraging length/height catch-up

Although several studies have shown that, even in the absence of any nutritional interventions, catch-up in linear growth may occur in some children if malnutrition is not the primary underlying cause,[23,59] the extent of height catch-up is highly context-specific and probably reflects food availability, dietary patterns, and the prevailing burden of infection, and is likely driven via epigenetic modifications.[23] In one non-interventional study in children from Ethiopia, India, Peru, and Vietnam, the incidence of recovery from stunting ranged from 27% (Vietnam) to 53% (Ethiopia) between the ages of 1 and 5 years, and from 30% (India) to 47% (Ethiopia) between the ages of 5 and 8 years.[59] As noted above, the high incidence of environmental enteric dysfunction may be a major reason for difficulties in achieving sufficient linear catch-up growth in children in low-income countries.[52]

Rather than adopting a 'wait-and-watch' approach, however, concerted efforts at intervention are crucial to optimize child outcomes. It has been shown that a good proportion of stunted children can achieve catch-up growth with improved healthcare and adequate nutritional support. For example, a longitudinal study of 6,800 Indian children adopted in Sweden at a mean age of 15 months, the majority of whom were chronically malnourished and stunted on arrival, showed a measure of catch-up growth and weight gain two years after arrival; although growth was not as rapid in stunted children as in those who were not stunted on arrival.[58] Most children in this study had good potential for recuperation; infection clearance was rapid, and the incidence of poor psychomotor development dropped from 29% on arrival

to 4.7% after two years, despite only limited catch-up in head circumference growth.[58]

To maximize the chance of catch-up growth, various nutritional programs and intervention strategies have been proposed and trialed in various countries. Such interventions have included promotion of breastfeeding, promotion of complementary feeding through parental education and/or food provision, and micronutrient supplementation,[18] each of which are discussed below.

Weight gain versus linear growth promotion: a balanced approach

Linear growth retardation is more difficult to correct than simple reduced weight gain.[44] Historically, community management of malnutrition has focused on weight gain during the period between 6 and 24 months, with little or no attention to linear growth.[32] However, wasting and stunting respond to different types of intervention, and it is important to consider both measures, especially in relation to later health outcomes.[30]

In **Chapter 5**, it was discussed how rapid early-life weight gain is associated with a higher risk metabolic diseases, including obesity, in later life. This also applies in low- and middle income countries with higher incidences of wasting. It is currently recommended that, due to these long-term risks, rapid weight gain should not be promoted after 2–3 years of age in children who are underweight but not wasted.[60] Instead, novel interventions that aim to specifically promote linear growth need to be developed and tested.[60]

> Due to the long-term risks of rapid childhood weight gain for adult health, rapid weight gain should not be promoted after 2-3 years of age in children who are underweight but not wasted.

Timing of interventions

Ideally, prevention of growth restriction should address causative factors as early as possible, which may be well before actual growth faltering can be diagnosed. Once stunting has developed, there are still relevant opportunities for nutritional intervention up to approximately the age of two years.[23,24,36,61] After this critical window of opportunity, recent evidence suggests that continued efforts to improve catch-up growth may still be justifiable, particularly in mid-childhood, although caution is needed to prevent long term adverse outcomes by relative overfeeding.[23,59] A large study in low- and middle-income countries showed that, for every standard deviation improvement in linear growth at the age of two, adult height increased by approximately 3 cm; and, for every further standard deviation improvement in height in mid-childhood, adult height increased by approximately 2 cm.[60]

> Ideally, prevention of growth restriction should address the causative factors as early as possible (including during the pre-conception period). Once stunting has developed, there are relevant opportunities for nutritional intervention up to approximately the age of two years. After this critical window of opportunity, recent evidence suggests that continued efforts to improve catch-up growth may still be justifiable, particularly in mid-childhood.

Nutritional interventions for stunting

Adequate nutrition is crucial for child development during the first 1,000 days, during which linear growth is the most sensitive to modifiable environmental factors.[20] The first two years of postnatal life thus represent an important opportunity for nutritional intervention.[23]

Whereas direct, age-appropriate nutritional interventions are the primary focus, on a global scale, nutrition intervention alone is unlikely to be sufficient to reduce stunting prevalence.[20] It is important to also acknowledge other key environmental and lifestyle aspects to achieve a reduction in stunting incidence, including education and empowerment of women, family planning, infection control, access to clean water and sanitation, and economic development.[5,20,36]

Systematic reviews of the effectiveness of nutritional interventions have shown a significant impact on behavior, but so far only modest and context-dependent benefits for height gain or stunting prevalence have been demonstrated.[18] Often, interventions start only after stunting has been diagnosed, which may be too late to leverage the full opportunity to improve length gain. However, one large, recent international study has estimated that global stunting in children under 5 years of age could be reduced by over 20% with optimal management of acute malnutrition, and delivery of appropriate nutrition packages and education, and micronutrient supplementation (assuming 90% coverage).[5]

1. Maternal nutritional supplementation during pregnancy

From the very start of the first 1000 days, optimal intrauterine growth needs to be protected by ensuring adequate maternal health and nutrition status and preventing and treating any maternal infections and complications, especially in low- to middle-income countries.[20,36]

There are few long-term studies evaluating the effects of prenatal macro- and micronutrient supplementation on subsequent child height, but overall the outcome data are inconsistent,[20,23] especially in low- to middle-income countries.

2. Infant/child nutritional management

Children with suspected compromised linear growth should, if possible, undergo a detailed evaluation to identify underlying causes.

Evaluation may include a combination of elements including personal, family, and social history, thorough physical examination, laboratory workup, radiological examinations, genetic testing, and consultation with a pediatrician or pediatric endocrinologist. Stunting with no apparent cause may be diagnosed as idiopathic short stature.[53] In countries where it is feasible, early identification of compromised growth and prompt referral to specialist care offers children the best opportunity for appropriate diagnosis, treatment, and optimal clinical outcomes.[53]

Prevention and control of (repeated) infection is considered to be an important complementary approach to stunting prevention, particularly in low- to middle-income countries.[5,20] Adequate nutrition can help reduce the negative impact of childhood infection by strengthening the immune system, providing extra amounts of nutrients to compensate for losses and to fuel catch-up growth, preventing poor appetite associated with micronutrient deficiencies, and encouraging the growth of beneficial gut bacteria to enhance gut function.[20]

Currently it is unclear whether nutritional intervention can directly improve neuro-developmental outcomes in stunted children.[5]

a) Promotion of breastfeeding

Despite the established benefits of early and exclusive breastfeeding for infant morbidity and mortality,[20,26,62] there are few longitudinal, randomized data demonstrating the specific benefits of exclusive breastfeeding for stunting prevention or intervention. A positive impact is plausible, given that exclusive breastfeeding helps protect against infection and diarrhea,[5,62] which in turn is likely to help promote linear growth.[5] However, cause-and-effect is difficult to establish,[20] and even infants who are breastfed may experience stunting or lack of linear catch-up growth.[30]

A well-conducted review of the available evidence, as well as a recent meta-analysis, were both unable to demonstrate any direct effects of

interventions to increase breastfeeding on stunting in low- to middle-income countries,[44,63] which may suggest a possible compromised micronutrient status that is, at least in part, translated to the mother's breastmilk,[64,65] and/or may be related to the high incidence of environmental enteric dysfunction or other chronic conditions among these infant populations.[20] Studies have shown that the secretion of several dietary micronutrients into human milk, particularly water-soluble vitamins such as thiamin, riboflavin, and vitamins B-6 and B-12, as well as vitamin A, can be improved through maternal supplementation. However, breast milk composition is relatively independent of maternal mineral status or intakes.[64]

Regardless, there is no apparent overall risk of growth deficits with exclusive breastfeeding during the first six months, and the WHO continues to recommend exclusive breastfeeding up to six months of age in both low- to middle-income and higher-income countries.[66,67]

b) Complementary feeding and food provision

The introduction of complementary foods presents an opportunity for nutritional intervention in stunted children, but outcome data are mixed. Studies encompass a wide array of dietary choices and practices, and populations have varying levels of "food security", making it difficult to draw strong conclusions.[5,20] It has also been postulated that the modest and inconsistent effects of nutrition interventions could be explained by the heavy infectious disease burden and high incidence of environmental enteric dysfunction in the low- to middle-income countries in which studies have been conducted.[23,52]

Most studies of maternal education regarding nutrition and complementary feeding as a sole intervention strategy have shown no, or only a modest, effect on linear growth. The effects appear to be slightly greater in food-insecure populations,[5,20,23] and in cohorts given specific educational messages, including regarding consumption of energy-dense or protein-rich foods.[30,68] In food-insecure populations, provision

of complementary foods with or without such nutritional education has been shown to modestly improve weight and linear growth,[5,23,44,69] highlighting the basic importance of food availability. However, beyond the age of 2 years, food provision programs evaluated to date have not appeared to significantly reduce stunting.[27]

Stunting interventions based on increasing the energy density of complementary foods have also yielded mixed results. It is thought that increasing energy density is likely to only be effective among infants whose traditional complementary foods have low energy density, and where infants are unable to compensate by sufficiently increasing food volume intakes.[20]

Dairy protein has been shown to have a specific stimulatory effect on linear growth in children in low- to middle-income countries, but also in industrialized countries where overall nutrient intakes are generally adequate.[70,71] However, unfortunately the cost of adding dairy products to the diet is prohibitive in some low-income countries.[70] Evidence suggests that cow's milk has a stimulating effect on plasma IGF-I,[70,71] and also directly stimulates growth through its high protein digestibility along with the presence of bioactive peptides, bioactive factors, and minerals such as potassium, magnesium, and phosphorous.[70,71] Addition of dairy protein to the diet also improves protein quality, making it possible to reduce the total dietary protein content, which has potential metabolic advantages.[71] However, it has also been noted that promotion of rapid growth by cow's milk through stimulation of bioactive components may have possible implications for noncommunicable disease risk in later life.[71]

c) Micronutrient interventions

Micronutrient fortification of complementary foods, as well as strategies to increase the bioavailability of key nutrients, have been shown to influence linear growth and weight gain in some studies but not in others.[5,20,23,36,72] A pooled analysis of four systematic reviews showed that preventive zinc supplementation reduced the odds of stunting by

15%, and reduced the risk of all-cause mortality by 9%, in children over the age of 6 months.[44] One comprehensive systematic review showed no direct reduction in stunting with vitamin A supplementation,[44] although a large study in India has shown a reduction in stunting risk in children who received vitamin A supplements at any time.[18] Vitamin A, like zinc, decreases the incidence of infectious diarrhea[5] which may have beneficial effects for nutrient retention.

There is also some evidence that micronutrient supplementation, particularly in low-to-middle income countries, may improve indices of cognitive performance, although the benefits are limited.[36]

It is thought that an adequate supply and balance of macronutrients is needed throughout the first 2 years of age to ensure a growth response to micronutrient supplementation.[20]

d) Other supportive strategies

Hygiene interventions (e.g. handwashing, water quality treatment, sanitation, and hygiene improvements) are expected to indirectly reduce the odds of stunting in low-to-middle-income countries, through a reduction in both the incidence of infectious diarrhea and the severity of environmental enteric dysfunction.[44]

In higher-income countries, the use of growth hormone has been employed in specific cases to encourage linear growth in stunted children. However, a discussion on the use of growth hormone is not within the scope of this book.

Wasting and severe wasting: Prevalence, causes, timing, impact, and management

Prevalence and burden of wasting

There is only a weak correlation between wasting and stunting in children under 2 years of age, and the prevalence of these two conditions is not necessarily geographically associated; countries with

similar stunting prevalence can show large variations in their respective wasting prevalence.[30]

Overall, wasting is less prevalent than stunting.

- Wasting currently affects approximately 8% of children worldwide, corresponding to a burden of approximately 50-52 million wasted children.[26,51] These data represent an 11% decrease since 1990, when the wasting burden was approximately 58 million (**Table 12**).[26]
- Approximately 70% of children with wasting reside in Asia,[26] with south-central Asia showing the highest prevalence (16%), followed by central Africa.[26,30]
- In 2011, the wasting prevalence in low-to-middle income countries versus high-income countries is approximately 9% versus 2%, respectively.[26] Of these children with wasting, 50% reside in India, but their national rate is decreasing.[4]

The 2011 estimated global prevalence for severe wasting was approximately 3% (19 million), but the incidence in higher income countries is well under 1%.[21,26,51] The highest percentages of children with severe wasting are found in central Africa and south-central Asia (6% and 5%, respectively; 2011 data), countries with serious challenges regarding food availability and security.

Recent international data indicate that the prevalence of newborn wasting (defined as less than the 3rd percentile of the INTERGROWTH-21st standards for BMI-for-gestational age) is 3.4%; 0.7% of newborn infants had both stunting and wasting.[9]

Risk factors for wasting

Risk factors for wasting are represented in **Figure 16**.

A pre-conception factor associated with childhood wasting is short maternal height, although the association is weaker for wasting than for stunting.[26]

Environmental factors include severe infectious diseases, which can cause acute wasting.[26] Chronic dietary exposure to mycotoxins has also been implicated in acute malnutrition/underweight.[46,47]

Timing of wasting, health risks, and interventions

Faltering in weight-for-length/height tends to begin between 3 and 12 months of age in infants born AGA at term,[23,32,36] and is usually restricted to the first 15 months, followed by rapid improvement.[15,23]

Wasting is associated with a higher risk of mortality in early childhood. As with stunting, generally younger children with more severe wasting are at greatest risk.[26,44]

As well as its benefits for linear growth, cow's milk has been shown to improve dietary protein quality and promote weight gain in children with wasting due to malnutrition.[70,71]

In children with severe wasting, more rapid weight gain may be achieved with a therapeutic diet, compared with other diets, leading to faster recovery.[21] Supplementary foods that are used as a main source of energy should be formulated in accordance with authority recommendations, with nutrients at levels that do not cause adverse effects for longer term consumption. A child's habitual diet must be taken into consideration when assessing the amount of supplementary food needed.

There are clear WHO guidelines both for inpatient and community-based treatments available for both SAM[72] and moderate acute malnutrition.[73]

A recent, large international study has estimated that, with 90% coverage, delivery of nutrition education, nutrition packages, and micronutrient supplementation could theoretically reduce severe wasting by over 60%.[5] Another study showed that, if severe wasting was managed according to WHO guidelines, the case-fatality rate would be reduced by 55%.[44]

In high-income countries, the treatment of wasting by way of clinical nutrition intervention is mostly based on detailed (local) guidelines and recommendations.

Chapter highlights

- Globally, stunting, wasting, and micronutrient deficiencies are estimated to collectively contribute to over 3 million childhood deaths annually.
- Stunting refers to poor linear growth, defined as low length/height-for-age, and is often a consequence of chronic under- or malnutrition. Wasting (thinness) refers to low weight-for-length/height, and is an indicator of acute malnutrition.
- Wasting prevalence and stunting prevalence are not necessarily geographically associated; in general, these two conditions have different risk factors, chronological patterns, and prognoses.
- Stunting risk may be attributable to factors present before conception, *in utero*, and/or after birth.
- Risk factors for stunting include:
  - Pre-conception: short maternal height; young *maternal* age; poor nutritional status.
  - Prenatal: fetal growth restriction; low gestational weight gain; maternal infections or subclinical conditions; smoking; drug use.
  - Postnatal: under- or malnutrition; hormonal factors; no or limited breastfeeding; infections (particularly diarrhea); parasitic infestations; environmental enteric dysfunction; chronic diseases; low household income; large family size.
- Risk factors for wasting include:
  - Pre-conception: Short maternal height (weak association).
  - Postnatal: Infectious diseases; mycotoxins; other conditions that impair food intake or nutrient absorption.
- Stunting is associated with a higher risk of impaired cognitive and motor development, persistent short stature, and lower educational and occupational achievement, and may lead to an intergenerational cycle of low birthweight. In low- and middle-income

countries, stunting is also associated with an increased risk of mortality in early life. When accompanied by rapid or excessive weight gain *after* the age of two years, stunted children may also be at increased risk of nutrition-related chronic cardiometabolic diseases in later life.

- Adequate and appropriate nutrition at the earliest possible opportunity is imperative for optimal child development during the first 1,000 days. To maximize the chances of early and adequate catch-up growth in stunted children, various nutritional education programs and interventions have been proposed and trialed around the globe, with varying levels of success.
- Historically, it has been accepted that the crucial window of opportunity for nutrition intervention to treat stunting was up to the age of 2 years; however, recent research indicates that later interventions may also be justified.

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Chapter 8

Overweight and obesity

In parallel with a global decrease in childhood underweight, the increasing prevalence of childhood overweight and obesity has been described as a global pandemic.[1–3] There are now more obese individuals than underweight individuals, both globally and in all regions of the world, with the exception of parts of Asia and sub-Saharan Africa.[4] As described in **Chapter 1**, many countries face a double burden of malnutrition within the same population, with high rates of both underweight/stunting and overweight/obesity.[3]

Childhood overweight/obesity has been shown to track strongly through adolescence and into adulthood,[5] and is associated with both immediate and long-term adverse health consequences.[2,6,7] Identification of early risk factors for obesity, and appropriate interventions for the prevention and management of childhood obesity, are therefore considered to be critically important public health priorities.

Defining child overweight and obesity

Overweight and obesity are defined as "abnormal or excessive fat accumulation that may impair health".[8]

Although only an indirect estimate for the amount of body fat, BMI is the currently accepted standard measure for the assessment of overweight and obesity in children and adults; although the prediction is more accurate for adults than for children.[9] In adults, definitions of overweight and obesity are a BMI of $\geq$25 and $\geq$30 kg/m^2, respectively;[8] although, lower cut offs have been proposed for persons of Asian ethnicity given their differences in body composition and associated metabolic disease risk.

In infants and children, such a global consensus definition for excess adiposity is lacking. Only the WHO provides definitions of overweight and obesity based on weight-for-length in infants and children between birth and the age of 2 years (more than 2 or 3 standard deviations above the median of the WHO Child Growth Standards, respectively).[10] This is also applied by the US Centers for Disease Control and Prevention (CDC).[11]

With regard to the use of BMI measurements in children, given the fact that infants and children are rapidly changing both in terms of weight and length, the value of BMI charts to evaluate excess adiposity in children is not entirely clear.[12,13] The WHO defines childhood overweight and obesity (from 5 years of age) as a BMI greater than 2 or 3 standard deviations, respectively, above the median of the WHO growth reference for BMI.[14] The CDC defines childhood overweight and obesity (between 2-19 years of age) as a BMI between the 85th and 95th percentile, or above the 95th percentile, respectively, of the age- and sex-specific CDC Growth Charts.[15] Finally, the international Obesity Task Force provides international BMI cut off points from 2 years of age by age and sex, corresponding to an adult BMI of 25 (overweight) and 30 (obesity).[16] Interestingly, the Obesity Task Force and CDC cut off points are lower compared with those defined by the WHO, resulting in differences in prevalence rates for childhood overweight and obesity in a given population.

Clearly, there is a need to harmonize international standards. The use of standardized definitions to establish excess adiposity is essential to enable early detection of growth deviations and intervention in infants at risk, which is key to supporting initiatives for the prevention of childhood overweight and obesity.

Prevalence of childhood overweight and obesity

In 2011-2014, approximately 41-44 million children worldwide under the age of 5 years (approximately 7%) were overweight or obese according to the WHO definition, representing an increase from 28-31 million in 1990.[6,17-19] The global prevalence of childhood overweight and obesity is expected to reach 10% in 2025, amounting to 64 million children.[6]

High-income countries have the highest prevalence of overweight (15% in 2011), but the absolute numbers of

overweight children are highest in low- and middle-income countries,[6] particularly in East Asia and the Pacific.[17]

Within low- to middle-income countries, the prevalence tends to be higher among higher-income sectors compared with lower-income sectors, and slightly higher in urban versus rural areas;[6] the opposite is often observed in high-income countries.

UNICEF and WHO data show a gradual increase in overweight prevalence in most regions, both in high income countries and low-to-middle income countries.[17-19] The greatest absolute and relative increases in overweight prevalence have been observed in central and eastern Europe, Africa, and Asia.[17-19] Numbers in Latin America and the Caribbean have remained relatively steady over the past two decades.[17] The current prevalence is approximately 7% in both Africa and Latin America, and around 5% in Asia.[6,19]

The prevalence was significantly higher among girls (11%) compared with boys (4%).[20] Another very recently published report has demonstrated modest progress in the control of under-5 obesity in the US, with a decrease of almost 4% (from approximately 12% to 8%) between 2009 and 2012.[21]

Indeed, there is some evidence that the prevalence of infant and childhood obesity may be reaching a plateau in some high-income countries.[22,23] However, the vast majority of the globally increasing number comes from the alarming increases observed in low- and middle-income countries.

Consequences of infant/child overweight and obesity

Childhood overweight and obesity are associated with both immediate and long-term health risks.[6]

Immediate health risks include metabolic abnormalities such as hypercholesterolemia, hypertriglyceridemia, impaired glucose metabolism, type 2 diabetes, high blood pressure, and fatty liver disease.[6] Moreover, obese children are at greater risk for the development of psychological or social problems associated with bullying experiences and adult depression.[24,25] The metabolic conditions are becoming already evident in childhood[26] with the majority of obese children showing at least one cardiovascular disease risk factor.[2] Increased childhood morbidity adversely affects childhood development and quality of life,[2] and obese children may also experience social stigma.[7]

At least two thirds of obese children remain obese as adults.[2,7] Adult obesity is associated with serious consequences in terms of its associated disease risks.[6,27] Non-communicable diseases such as diabetes, cardiovascular disease, and the metabolic syndrome account for around 60% of all deaths worldwide.[27]

> Childhood obesity tends to track closely from childhood through adolescence into adulthood . . . at least two thirds of obese children remain obese as adults.

Risk factors for obesity development

The etiology of obesity is multifactorial, with a range of environmental, genetic, and physiological contributing factors beginning during, or even before intrauterine life.[7,28] Hence, it is important to acknowledge the entire life course, since it is well established that developmental trajectories early in life can influence an individual's response to later environmental exposures – the so-called intergenerational cycle of obesity.[27,29] Moreover, it can also influence the next generation.

Key risk factors for the development of obesity are summarized in **Figure 18**. Many of these factors are modifiable, and thus present important opportunities for early prevention.

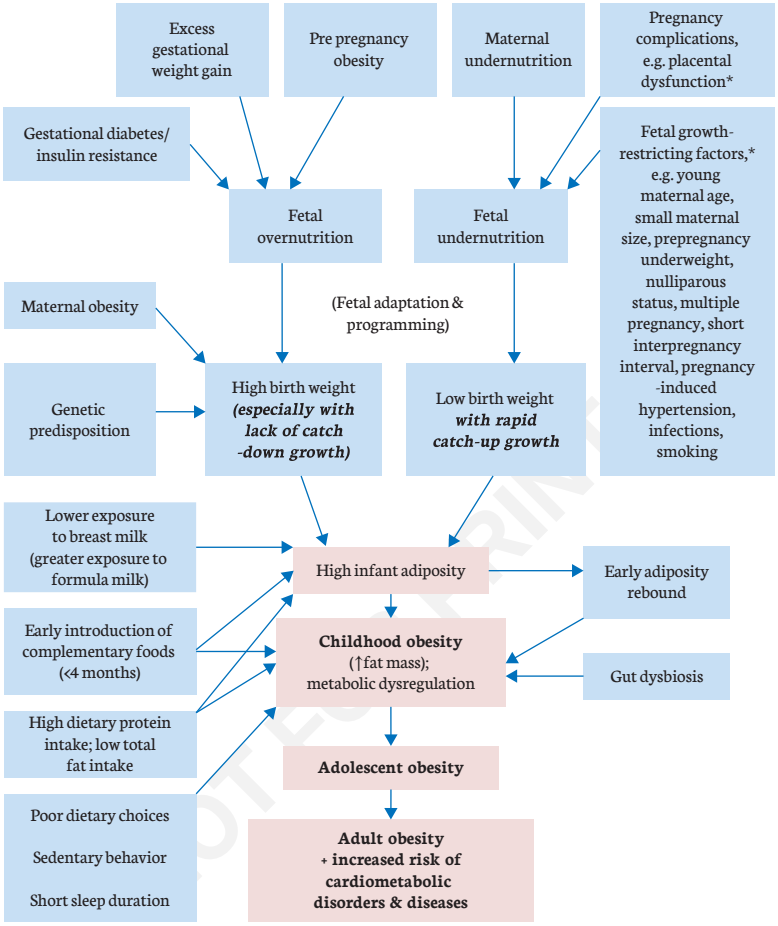

Figure 18. Overview of risk factors for obesity from intrauterine life to adulthood

*See Chapter 5 (SGA chapter) for more information.

Genetic predisposition

Obesity in either parent is a strong predictive factor for childhood obesity, and a genetic predisposition toward positive energy balance and obesity has been identified.[2,5,7] Yet, although over 50 genetic variants associated with obesity have been now identified, these explain only 1-2% of the normal variation in BMI.[30,31] Evidence from the large

Avon Longitudinal Study of Parents and Children (ALSPAC) UK birth cohort study showed a three- to four-fold increased risk of obesity at the age of seven years if only one parent was obese, and a ten-fold increase if both parents were obese.[32] This indicates the importance of both environmental factors and the gene-environment interaction in the development of overweight and obesity.

Clearly, genetics alone cannot explain a propensity toward obesity. As an example, the BMI of children born to recipients of egg donation has been shown to be closer to the recipient mother's BMI than the donor's BMI, illustrating the fact that the intrauterine environment may play an even stronger role than genetic predisposition.[7] In addition, studies in countries such as Chile, which has undergone a rapid nutritional, demographic, and socioeconomic transition in the past three decades resulting in greatly increased rates of child obesity, but with little change in the gene pool, suggest that obesogenic environments are more directly responsible for obesity than genetics.[33] Indeed, the latest findings from genome-wide association studies suggest that only 2.7% of the normal variation in BMI can be explained by genetic traits.[34]

It seems more likely that the propensity toward obesity may be explained by epigenetic mechanisms altering organ development and gene function,[27,28] and there is even some evidence for their perpetuation through the intergenerational cycle.[27,35]

Fetal overnutrition

The DOHaD hypothesis, discussed in **Chapter 2**, has described the link between prenatal (and early postnatal) environmental exposures and the subsequent development of obesity and nutrition-related diseases.[7] Although most literature supporting the DOHaD hypothesis relates to fetal adaptations to maternal *undernutrition*, resulting in a "thrifty phenotype" and increased cardiometabolic risks, it is now becoming widely recognized that these increased health risks in adulthood also stem from the other end of the spectrum – fetal overnutrition.[7]

Fetal overnutrition may result from high pre-pregnancy maternal BMI, excess gestational weight gain, or gestational diabetes. Fetal adaptations may result in increased growth relative to an individual's genetic potential, and can thus result in a relatively high birth weight. High birth weight shows a strong positive association with both childhood and adult overweight,[5,32,36] and may predispose an individual to obesity-related chronic diseases.[2,7,36]

However, a high birth weight, as such, is not always an indication of fetal overnutrition. An infant might simply be constitutionally large at birth, for example, due to tall parental height. It should be noted that, while many studies show a general association between birth weight and later obesity, most do not take into consideration the differential associations between birth weight and later body composition,[5] nor the body composition of an infant at birth and its association with the postnatal growth trajectory. In general, high birth weight has been shown to be associated with both increased lean body mass and adiposity.[5] Also, studies using child or adult BMI as an endpoint may not account for the fact that different growth trajectories are associated with different patterns of body composition development, and that fat accumulation in different body compartments could result in the same BMI, but different metabolic development/function, at a given time point.[5] Further studies are needed to fully elucidate these issues and better understand the interplay between high fetal growth and overweight and obesity later in life.[5]

Maternal pre-pregnancy obesity is known to be a strong risk factor for high birth weight, rapid early-life weight gain, childhood obesity, increased fat mass development, and metabolic dysregulation.[2,7] The direct relationship between maternal obesity and child obesity has been demonstrated in two studies comparing the offspring born to women pre- versus post-weight loss surgery. Significant reductions in the prevalence of infant macrosomia and downstream obesity were observed among children born after the mother's surgery,

compared with their siblings born before surgery.[2] This is particularly interesting, given that, under normal circumstances, increasing birth order tends to result in *increasing* birth weights.[37–40]

Independent of maternal BMI, gestational weight gain is positively associated with birth weight, infant adiposity, and risk of overweight throughout childhood and adulthood.[2,5,7,41,42] These associations appear to also be independent of genetic predisposition, and are particularly strong among women who had a high pre-pregnancy body weight.[2,7,43,44]

> Maternal obesity, excess gestational weight gain, and maternal hyperglycemia have been strongly implicated in fetal over-nutrition, and are believed to have fetal programming effects for obesity and cardiometabolic risks in later life.

Pregnancy induces a normal physiological state of insulin resistance and changes in lipid levels and metabolism to support normal fetal growth, but these changes are more pronounced and occur earlier during the course of pregnancy when a woman is obese.[45] It is thought that pregnancy-induced alterations in metabolic set points may account for a significant proportion of fetal adiposity and postnatal obesity.[7]

The Institute of Medicine (IOM) guidelines acknowledge the above risk factors, and recommend that women who are overweight or obese prior to pregnancy should aim to gain less weight during pregnancy than their leaner counterparts (see **Table 13**).[46,47]

Postnatal growth

Rapid linear growth in the first two years, which often occurs as catch-up growth in infants born with low birth weight or SGA, is associated with increased fat mass accumulation during childhood, and a higher risk of becoming overweight.[5,7,48,49] This impact of rapid early growth

on adiposity and/or obesity development has been demonstrated in both high-income and low-to-middle-income countries.[48,50] Specifically, catch-up growth appears to be associated with increased central (abdominal) adiposity.[5,48]

Conversely, a lack of catch-down growth in infants with high birth weight has also been associated with increased adiposity and obesity risk.[2,51,52] Interestingly, a recent study in infants of mothers with gestational diabetes showed that adiposity in early infancy is amplified, even after good glycemic control during pregnancy, and despite predominant breastfeeding.[53]

Although the association between rapid growth in the first two years and overweight risk is well established, a large longitudinal study following children yearly showed that a rapid BMI increase at *any* time point during the first eight years was significantly associated with overweight risk at the age of eight years; there was no evidence for a specific critical time period for the development of overweight.[54] However, rapid increases in BMI or body weight are more common during the period of rapid growth during infancy and early childhood, and are more likely to be the result of adjustment towards an individual's genetically predetermined potential growth trajectory.

Early-life nutrition

An infant's growth and development is strongly driven by nutrition in the first two years. Apart from lean body mass accretion, it is known that the absolute number of adipocyte cells in each individual is established during early childhood; in adulthood, the number of fat cells stays rather constant, but the amount of lipid storage within the cells changes with weight loss or gain. It is thought that early nutritional exposures can cause permanent changes in absolute adipocyte numbers, supporting the idea that interventions to prevent obesity during childhood may help to decrease final numbers of fat cells – with possible implications for susceptibility to adult obesity.[55-57]

Breastfeeding

Growth patterns among formula-fed infants differ substantially from those of breastfed infants. Faster infant growth, particularly during the second half of the first year, is associated with higher BMI at one year of age. Indeed, numerous studies and two recent meta-analyses have shown breastfeeding to be protective against the development of childhood overweight and obesity,[58–60] and/or to promote a growth trajectory thought to protect against later obesity.[61–63]

> The protective effects of breastfeeding against obesity have been demonstrated in low-, middle- and high-income populations.

While some studies do not confirm these associations, this may be the result of differences between confounding factors (e.g. differences in how breastfeeding is assessed, or breastfeeding 'dose effects'), statistical methods, or varying study endpoints.[5,64,65] Conclusive evidence on this issue is difficult to obtain, as it is not ethical to randomize infants to breast- versus formula-feeding.

The underlying mechanisms for the potential protective effects of breastfeeding against childhood obesity are probably multifactorial. Apart from strong confounders such as maternal BMI, socioeconomic status, and maternal smoking, breastfeeding and human milk might be associated with characteristics favoring a healthy growth pattern. Breast milk increases in fat content during a nursing session, which might influence the development of the food intake regulation system in infants. Human milk also contains hormonal factors such as insulin and leptin, which may regulate early growth patterns, including adipocyte development. Protein levels in breast milk naturally decrease over time, and mature milk has a protein content that is lower than that of current formula milk; higher protein contents in formula milk have been suggested to promote excess adiposity gains by inducing increased insulin secretion.[5] One interventional study has shown that formulas with excessively high protein content (2.9 g/100 kcal up

to 4 months and 4.4 g/100 kcal from 4-12 months) encourage greater weight gain than those with a lower protein content (1.8 g/100 kcal up to 4 months and 2.2 g/100 kcal from 4-12 months).[66,67]

Early dietary patterns

As the infant makes the transition to solid food, dietary patterns are also important to consider in the development of obesity.

> Earlier weaning to solid foods (<4 months of age) is associated with increased obesity risk.

In addition, higher total energy consumption and higher protein intakes in early life appear to be associated with an increased risk of overweight and obesity in adulthood.[69,70]

The percentage of energy from carbohydrates in early life has shown a positive association with adult adiposity.[64] High childhood protein intakes also appear to be associated with body fat development in some studies,[64,71] but not in others.[72]

With regard to the effect of total fat intakes and specific fatty acid compositions during the weaning period, the evidence is less clear.[64,73] A French longitudinal study demonstrated that low fat intakes in early life (measured at 10 months and 2 years) were associated with increased adiposity in adulthood;[64,69] this finding is similar to outcomes from other studies in different contexts, suggesting that fat restriction and/or high protein diets in early life may program overweight in later life.[64,74] It is generally accepted that infants should not receive low fat diets during complementary feeding, as their energy requirements remain high during this period.

There is also emerging evidence of the effect of worldwide *qualitative* changes in fatty acid intakes during the past few decades, due to both indiscriminate dietary choices to substitute PUFAs for saturated fats, and changes in animal feeding practices which influence

the food chain. These changes affect both breast and formula milk fat compositions, as well as solid foods, and evidence is emerging from animal and human studies that changes in the overall balance of essential PUFA intakes may influence adipogenesis as well as the conversion rate of pre-adipocytes into mature adipocytes during the early stages of adipose tissue development.[73]

There is concern that, in many countries, the transition from an exclusive milk diet to family meals may involve the early introduction of highly processed and sweetened foods, encouraging the innate preference for an energy-dense, nutrient-poor diet.[75] Advertising of such foods to older children is of concern in both high income and low-to-middle income countries, and may undermine parental efforts to offer healthy foods to their children.[75]

Role of the gut microbiota

Infancy is a critical period during which a range of factors influence the colonization and development of the gut microbiota.[76] As discussed in volumes 1 and 2 of this book series, a disrupted gut microbiota (termed 'dysbiosis') appears to play a role in the development of obesity. This association appears to be independent of other established obesity risk factors.[76] Further discussion on this topic is outside the scope of this book.

Early adiposity rebound

In **Chapter 2**, we briefly described how infants tend to reach a peak in BMI at approximately 6-9 months of age after a rapid period of adipose tissue growth.[62,77] The height of this BMI peak is positively associated with childhood BMI.[78]

While in this book we focus on the first two years, it should be noted that a BMI nadir – termed an 'adiposity rebound' – occurs usually between the ages of 5 and 7 years.[74,77] The timing of this adiposity rebound has been shown to be inversely associated with adult

obesity.[32,74] In longitudinal studies, an earlier adiposity rebound (at approximately 3 years) is recorded in the majority of obese adults, compared with lean individuals who show an adiposity rebound at approximately 6 to 7 years.[74] Earlier adiposity rebound is also associated with increased fat deposition in middle childhood through to adulthood.[79] The striking difference in mean age at adiposity rebound between obese and lean individuals confirms the involvement of nutritional factors very early in life, and highlights the importance of monitoring children throughout childhood.[74]

Obesity prevention: Targeting modifiable risk factors during pregnancy

Because obesity is very difficult to correct once established, and childhood as well as adult lifestyle interventions for metabolic disease can be ineffective,[80] earlier preventive efforts employed during the period of greatest developmental plasticity – rather than waiting for obesity and its related diseases to manifest – are of paramount importance (**Figure 19**).[81]

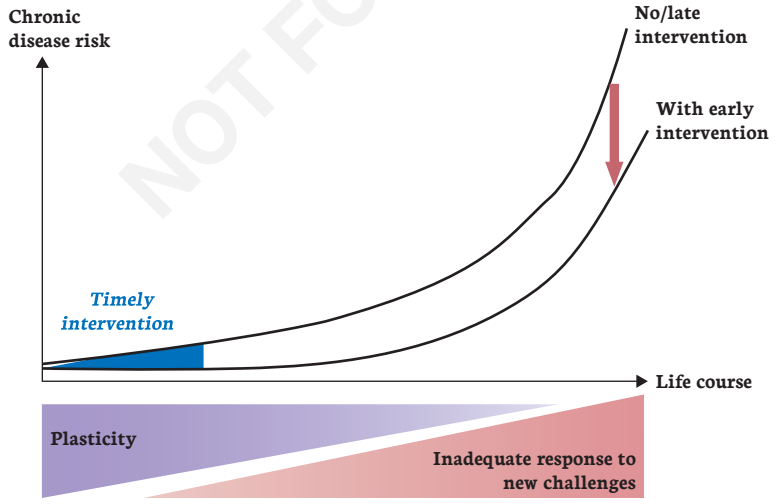

Figure 19. Importance of early intervention during the period of greatest developmental plasticity with regard to chronic disease risk in later life[27]

Adapted with permission from: Godfrey et al. *Trends Endocrinol Metab.* 2010; 21: 199–205.

Thus, promotion of lifestyle behaviors that encourage optimal fetal, infant, and child growth and development and take into account intergenerational effects have important implications for the prevention of non-communicable diseases. This is especially important among populations undergoing rapid socioeconomic transition.[27]

> Because obesity is difficult to treat once established, and childhood and adult lifestyle interventions for metabolic disease can be ineffective, earlier preventive efforts employed during the period of greatest developmental plasticity – rather than waiting for obesity and its related diseases to manifest – are of paramount importance.

Taken together, the body of evidence suggests that interventions aimed at pregnant women with the intent to encourage a more optimal intrauterine environment may be vital to improving both maternal and child health outcomes.[2,36] Indeed, several international and national health bodies, including the WHO, the U.S. Institute of Medicine, and the U.K. government have identified prevention of childhood obesity as a key priority, acknowledging the intrauterine period as a primary target for intervention.[2] In most cases, pregnant women are highly motivated to make positive behavioral changes for the wellbeing of their unborn infants.[2]

Maternal nutritional interventions

Half of women of childbearing age in the UK and two-thirds of those in the US are overweight or obese.[2] While these data are country-specific, maternal pre-pregnancy weight status is a clinically important global consideration from both an individual and a public health perspective.[2]

While there is strong evidence supporting the importance of the intrauterine environment for downstream obesity and the metabolic

syndrome, studies evaluating the effect of maternal dietary interventions during pregnancy with regard to downstream child or adult obesity outcomes are scarce.[2] To properly design and implement efficacious intervention strategies, there is a need for further well-designed, appropriately powered, prospective studies with standardized interventions and endpoints, and proper adjustment for confounding factors.[2]

Nevertheless, targeting maternal behaviors that lead to chronic fetal exposure to surplus energy and inappropriate metabolic hormone levels should be encouraged, because high maternal caloric intake, poor dietary composition, and sedentary behavior have been specifically identified as predictive factors for maternal obesity and excessive gestational weight gain.[2]

Targeting maternal behaviors that lead to chronic fetal exposure to surplus energy and inappropriate metabolic hormone levels should be encouraged, because high maternal caloric intakes and sedentary behaviors have been specifically identified as predictive factors for maternal obesity and excessive gestational weight gain.

A balanced diet, including high intakes of fruit and vegetables, moderate protein intakes from animal sources, and low or absent intakes of energy-dense, nutrient-poor foods with high sugar or saturated fat, is known to be beneficial for both the mother and the developing fetus.[2] The historical adage of "eating for two" during pregnancy is no longer accepted; it is now well established that, during pregnancy, changes in metabolism result in more efficient absorption and utilization of nutrients, meaning that the actual need for increased daily caloric intakes is minimal – only approximately 300 kcal extra during the third trimester, not taking into account potential progressive reductions in activity during pregnancy.[2]

A good proportion of studies evaluating nutrition interventions such as dietary advice and coaching have shown less weight gain during pregnancy in women receiving interventions, compared with control groups.[2] With regard to birth weight, one study in women following individualized diet plans based on their pre-pregnancy BMI had fewer perinatal complications and a lower incidence of LGA or macrosomic births compared with controls.[2]

It is important to also to consider the *quality* of nutrition, to ensure the developing fetus receives all necessary nutrients in order to thrive. Pregnancy increases the requirement for certain micronutrients (e.g. folic acid, thiamine, and riboflavin) and vitamins (e.g. A, C, and D).[2] Notably, obesity during the childbearing years is associated with lower vitamin D levels, which may increase the risk of insulin resistance in a woman's offspring.[2]

Interventions for sedentary maternal behaviors

Women who exercise regularly before pregnancy tend to weigh less, and the available evidence suggests that continuing to exercise is an important component of achieving a healthy pregnancy.[2]

The consensus is that regular moderate exercise during pregnancy, appropriately tailored to the stage of pregnancy, does not appear to increase the risk of adverse pregnancy or neonatal outcomes or compromise fetal growth. In fact, exercise appears to be associated with more healthy levels of gestational weight gain, as well as a reduction in the risks of gestational diabetes, high blood pressure, pre-eclampsia, varicose veins, and lower back pain.[2] Physical exercise also appears to protect against birth weight extremes (SGA or LGA), which is likely to positively influence downstream health in the child. This protective effect on birth weight is thought to be mediated by improved placental blood flow and function.[2]

However, just as with nutrition, physical exercise during pregnancy should be closely monitored.[2]

Table 13. Institute of Medicine (IOM) guidelines for gestational weight gain, based on pre-pregnancy weight:[47]

Weight category	Recommended total weight gain over duration of pregnancy	Recommended rate of weight gain during 2nd and 3rd trimester
Underweight (<18.5 kg/m^2)	12.5-18 kg	0.51 kg/week
Normal weight (18.5-24.9 kg/m^2)	11.5-16 kg	0.42 kg/week
Overweight (25-29.9 kg/m^2)	7-11.5 kg	0.28 kg/week
Obese (≥30 kg/m^2)	5-9 kg	0.22 kg/week

Recommended gestational weight increases are usually dependent upon pre-pregnancy BMI (**Table 13**).[47] Smaller absolute weight gains are recommended for overweight and obese mothers compared with normal-weight or lean mothers.[2]

Overall, average gestational weight gains have increased from 10 to 15 kilograms over the past four decades, and increases above the recommended weight gain ranges are particularly frequent among women with a high pre-pregnancy BMI.[2] It has been suggested that the current gestational weight gain guidelines may not be sufficiently conservative, and that even greater restriction in weight gain patterns may serve to improve maternal and fetal outcomes, if achieved.[2] However, there are no intervention studies to date showing a reduction in the risk of LGA or macrosomic birth through reduction of gestational weight gain in women with pre-pregnancy obesity.

Obesity prevention: Targeting modifiable risk factors after birth

Interestingly, animal models suggest that it is possible for epigenetic processes to be reprogrammed by dietary or endocrine means,[28,81] suggesting that interventions in early childhood may not be futile even if the intrauterine environment was suboptimal.

Nutrition in infancy and childhood

As demonstrated in our discussion of obesity risk factors, breastfeeding according to WHO recommendations should always be encouraged, as this practice has been shown to promote a more optimal growth trajectory with regard to the prevention of obesity and adverse health outcomes in later life.[61–63,82] Breastfeeding promotion may be especially important in overweight and obese mothers, who are less likely to breastfeed, and may breastfeed for shorter periods.[7] A recent study has shown that breastfeeding duration can be improved in this group of women through ongoing support.[83]

As discussed above with regard to complementary foods, solids should not be introduced before 4 months of age. Offering highly processed, sweetened, nutrient-poor foods or juices and sugar-sweetened beverages should be avoided.[84] Children should be offered a balanced diet consisting of simple foods, including high intakes of fruit and vegetables with moderate high-quality protein and carbohydrate intakes.

It has been suggested that early dietary manipulation of the gut microbiota through the use of prebiotics, probiotics, or synbiotics may help prevent or modulate the development of obesity. Several recent studies have shown a reduction in BMI and other anthropometric measures of adiposity in overweight children receiving probiotics or synbiotics.[76] A few studies have suggested that these children may be at risk for dysbiosis, although the direct benefits of infant probiotic or prebiotic supplementation for obesity prevention are inconclusive. Research is ongoing in this regard.[76]

Childhood lifestyle behaviors

Systematic reviews of child obesity prevention studies generally suggest that the most sustainable and beneficial effects result from multifaceted strategies focusing on nutrient-rich meals, preschool and school classroom education and activities, sports activities, and the involvement of home, (pre)school, community, and government.[75]

Table 14. Dietary and lifestyle guidelines for obesity prevention or intervention in infancy and early childhood

- Breastfeed according to WHO recommendations (exclusive or predominant breastfeeding for 6 months, and continuation of breastfeeding until at least 12 months of age)[61,85]
- Offer complementary foods by 6 months of age but not before 4 months[61,85]
- Ensure a balanced diet consisting of simple, nutrient-rich foods
  - Not advisable to restrict dietary fats in early life[64,74], although avoidance of excess saturated fat intake is advisable[86]
  - Encourage high intakes of fruit and vegetables,[84] with moderate (not high[64]) high-quality protein intakes, and moderate carbohydrate intakes
  - Avoid highly processed, sweetened, nutrient-poor foods and sugar-sweetened beverages[84,86]
- Encourage an active lifestyle; discourage sedentary behaviours such as television viewing[75,84]
- Encourage adequate nightly sleep duration (>10.5 hours[32])

Evidence also suggests that an adequate nightly sleep duration is also important for the prevention of obesity.[87]

Monitoring of weight status

It is important that primary care providers routinely assess children for overweight risk, in order to promptly identify poor dietary and activity habits and high weight or BMI.[84]

In infants and young children, serial anthropometric measurements should be taken and plotted against an appropriate growth reference chart, with particular attention to any growth trajectory that deviates from the expected curve or crosses a centile band. One large meta-analysis showed that the upward crossing of at least one weight centile band (e.g. 2nd to 9th centile, or 9th to 25th centile) between birth and the age of 2 years was associated with a 2-3-fold increase in the risk of overweight or obesity in later life.[5]

Expert Committee recommendations are that all children undergo BMI assessments at least annually, and that this data should be integrated with other information such as growth patterns, family history of obesity, and medical risks.[84]

Expert Committee recommendations are that all children undergo BMI assessments at least annually, and that this data should be integrated with other information such as growth patterns, family history of obesity, and medical risks.

Obesity is difficult, but not impossible, to correct once established. Healthcare professionals play a key role in providing obesity prevention education for all children, and suggesting weight control interventions in those carrying excess weight.[84] Regardless of prior history or environmental conditions, families should be counseled regarding specific lifestyle behaviors and dietary choices that can help prevent and correct overweight and promote the maintenance of healthy weight.[84]

Chapter highlights

- Definitions for overweight and obesity in children under the age of 2 years are not generally based on BMI. The WHO defines overweight/obesity in young children as weight-for-length/height greater than 2 standard deviations above the mean of the WHO international growth standards.
- In 2014, approximately 41-44 million children worldwide under the age of 5 years (approximately 7%) were overweight, an increase from 28-31 million in 1990. The global prevalence of childhood overweight is expected to reach 10% in 2025, amounting to 64 million children.
- Childhood obesity has been shown to track strongly through adolescence and into adulthood, and is associated with both immediate and long-term adverse health consequences. Childhood health risks include metabolic abnormalities such as hypercholesterolemia, hypertriglyceridemia, impaired glucose metabolism, type 2 diabetes, high blood pressure, and fatty liver disease. These conditions, as well as cardiovascular disease and the metabolic syndrome, are also associated with obesity in adulthood.
- Risk factors for childhood obesity include:
  - Pre-conception factors, e.g. genetics, pre-pregnancy BMI.
  - Gestational factors leading to fetal overnutrition, e.g. maternal obesity, excess gestational weight gain, maternal hyperglycemia.
  - Postnatal anthropometrics, e.g. high birth weight (especially without postnatal catch-down growth), rapid postnatal growth, high first BMI peak, and early BMI nadir (adiposity rebound).
  - Nutritional factors, e.g. lack of breastfeeding, and inadequate nutrition after weaning. High protein intakes, high carbohydrate intakes, and fat restriction during infancy appear to be associated with increased body fat development in some studies.
  - Lifestyle factors, e.g. sedentary behaviors and short nightly sleep duration.

- Because obesity is difficult to correct once established, early-life preventive efforts employed during the period of greatest developmental plasticity are of critical importance.
- Maternal pre-pregnancy weight control is important, and the intrauterine period is thought to be a primary target for intervention. Nutrition and closely monitored exercise interventions for pregnant women should aim to limit gestational weight gain within appropriate limits and reduce the risk of hyperglycemia.
- Breastfeeding of infants should be encouraged according to WHO recommendations. Infants and young children need a balanced, nutrient-rich diet consisting of a high intake of fruits and vegetables and moderate high-quality protein intakes, without early fat restriction. Avoidance of highly processed, nutrient-poor foods and sugar-sweetened beverages is important, and an active lifestyle with adequate sleep should be encouraged.
- Obesity is difficult, but not impossible, to correct once established. Children should be regularly monitored through anthropometric measurements, with dietary and lifestyle advice given to all caregivers and parents, even when a child's weight is within the normal range.
- Expert recommendations for older children, including those who are overweight, include avoidance of sugar-sweetened beverages, junk foods, and fast foods; eating breakfast daily; eating balanced, portion-controlled meals at home with the family, including high fruit, vegetable, fiber, and calcium intakes, engaging in moderate-to-vigorous physical activity $\geq$60 minutes per day, and limiting screen time.

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Chapter 9

Future directions

In this volume of the Essential Knowledge Briefing series, we have explored growth and body composition during the first 1,000 days. This represents a critical period of body growth and organ development, during which nutritional and other environmental insults and challenges may compromise a child's genetically determined growth trajectory. We have also highlighted that periconceptional factors can influence both prenatal and postnatal growth.

Evidence for the short- and long-term effects of early growth deviations is accumulating, fuelling the need to more fully understand the drivers and underlying mechanisms of growth and body composition development in various settings.

Understanding optimal growth

First, there is a clear need for a greater understanding of "growth". One fundamental need is to further define "optimal" growth parameters in relation to short- and long-term outcomes in different settings – for example, in low-to-middle- versus high-income populations, and in different populations of infants, such as those born SGA, LGA or preterm.

Measurements of weight and length (and additionally head circumference, at least during the first 2 years) are routinely used to evaluate growth, but it is also important to improve our understanding of the pre- and postnatal development of body composition (e.g. fat and lean body mass) and its association with health outcomes. This is relevant for term infants with a normal birth weight, as well as for infants born with a high or low birth weight, those born from complicated pregnancies (e.g. gestational diabetes and obese pregnancies), and those born prematurely. It is becoming clear that body composition is a more accurate predictor of later short- and long-term term (cardio-metabolic) outcomes than weight, length, and weight-for-length/height. This knowledge highlights the need to develop and

validate more simple, reliable, and standardized tools to accurately evaluate body composition in routine clinical practice, as well as in large cohort studies.

The use of standardized growth charts during both the fetal and postnatal periods is supported by the fact that, under optimal conditions, growth is remarkably comparable between populations. This was illustrated in the INTERGROWTH-21st and WHO growth standard studies, as previously discussed. Using the same growth charts in different populations would certainly facilitate our understanding of growth drivers and underlying mechanisms from a research perspective. However, the value of using standardized growth charts in clinical practice needs further evaluation in different settings, especially in situations where maternal and infant environmental conditions are suboptimal.

We also need a better understanding of the importance of nutrition and other lifestyle factors before and during pregnancy, as well as during lactation, and how these influence growth. In addition, further studies on the hormonal regulation of early growth are needed – specifically, what determines changes in hormonal growth drivers, and how do they interact? The roles of IGF-I and insulin have been described briefly, but emerging data indicate that leptin and the appetite-regulating hormones, adiponectin and ghrelin, may also play important roles in determining growth and body composition.

As highlighted, there is strong evidence that high growth velocity in early life is associated with an increased risk of later obesity and noncommunicable diseases. There is a need to more clearly determine the age period(s) during which high growth velocity most strongly affects later health outcomes; to what degree – and how – this association is driven by body composition (lean mass versus fat mass); and whether linear growth velocity plays a role in this association. By determining the degree to which this association is present in undernourished children, and in those born SGA or preterm, we will be able to more

precisely define the optimal velocity of catch-up growth in each situation with respect to short- and long-term health outcomes.

As discussed in the first two volumes of this Essential Knowledge Briefing series, emerging evidence suggests that the gut microbiota may play an important role in growth and long-term outcomes. Gut dysbiosis (i.e. a disrupted microbiota balance) appears to be associated with a number of adverse consequences, including obesity. Ongoing and future research is needed to further elucidate the factors that determine the development of the gut microbiota, what constitutes an 'optimal' microbiota composition in different circumstances, and how the microbiota influences growth, growth velocity, and body composition development.

Establishing appropriate interventions

Second, further research is needed to better understand possible opportunities for intervention in different at-risk situations and settings, in order to prevent or rectify suboptimal growth patterns.

In the first instance, there is a need to more fully establish best clinical management practices with regard to maternal interventions, as well as the timing of such interventions, to reduce the risk of compromised birth outcomes. For example, what are the most appropriate interventions to prevent or normalize high fetal growth velocity in cases of maternal gestational diabetes or obesity? How do we best ensure optimal fetal growth in pregnant women at risk of giving birth to an SGA infant? Ongoing research seeks to answer these and other questions, including how intrauterine growth goals and maternal clinical and nutritional management approaches should vary between low- and high-income countries.

More longitudinal data are also needed to establish the most appropriate intervention opportunities during infancy and early childhood, to prevent or rectify compromised growth. For example:

- How can we achieve optimal postnatal growth in preterm, SGA and LGA infants to ensure organ development and maturation without the potential detrimental long-term consequences of rapid (catch-up) growth?
- What are the most appropriate clinical and/or nutritional interventions for childhood stunting, wasting, and overweight/obesity?
- What age periods are most appropriate for the implementation of these clinical and nutritional interventions?

Further longitudinal data are also needed to establish how such interventions might influence health outcomes in the long term, and what the implications are among different populations.

Ongoing research aims to further understand the role of infant feeding, complementary feeding, and environmental conditions in different settings and in different groups of infants. Notably, in low- and middle-income countries, the fact that only modest effects have been demonstrated to date with nutrition interventions among populations with moderate-to-severe undernutrition is likely to be partially attributable to the widespread presence of subclinical environmental enteric dysfunction, underlining the importance of concurrent interventions to ensure adequate hygiene, sanitation, and appropriate health care provisions in such populations.

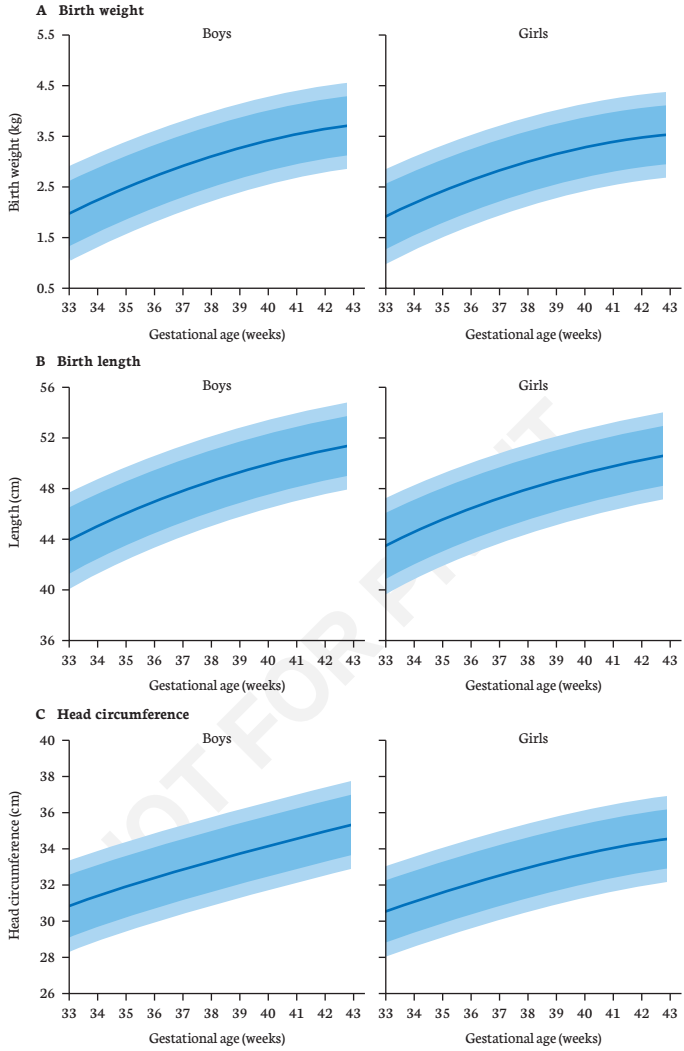
Conclusion

In summary, this volume outlines our current understanding of factors that influence the pre- and postnatal growth trajectory, and the implications of growth patterns, growth velocity, and body composition during the first 1,000 days on short- and long-term outcomes. It emphasizes the need for simple, reliable, standardized tools to evaluate body composition in particular, and for further research to establish the most effective prevention and intervention strategies in

infants and children at risk of compromised growth. Evaluation by validated pre- and postnatal growth charts is essential to understand the potential of such interventions to prevent stunting, overweight/obesity, and other long-term adverse health outcomes.

It is expected that ongoing collaborative worldwide research efforts will increase our understanding of pediatric growth and appropriate intervention strategies in at-risk individuals and populations. Addressing the unmet needs highlighted above will greatly help to improve national and global progress toward achieving the WHO's six key global nutrition targets for mothers and young children by 2025.

Appendix

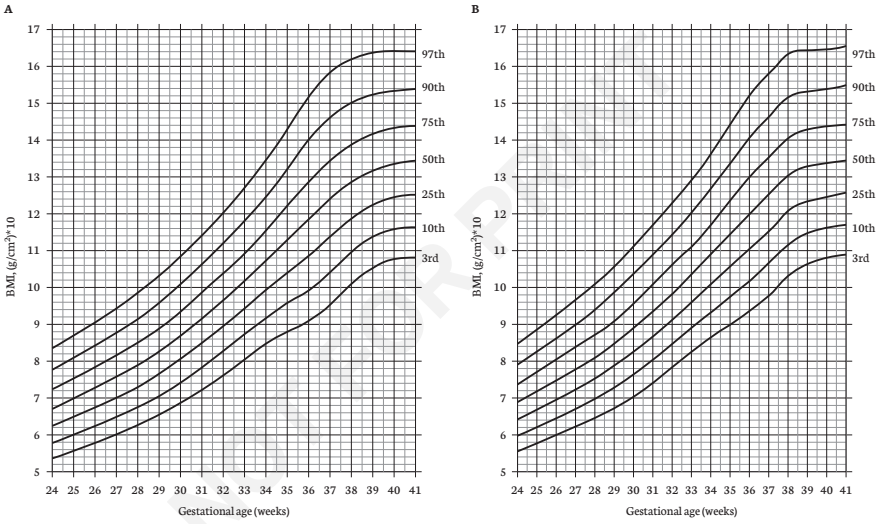


International fetal growth standards for birth weight, birth length, and head circumference (INTERGROWTH-21st Project)*[1]

3rd, 10th, 50th, 90th, and 97th smoothed centile curves for (A) birthweight, (B) birth length, and (C) head circumference according to gestational age.

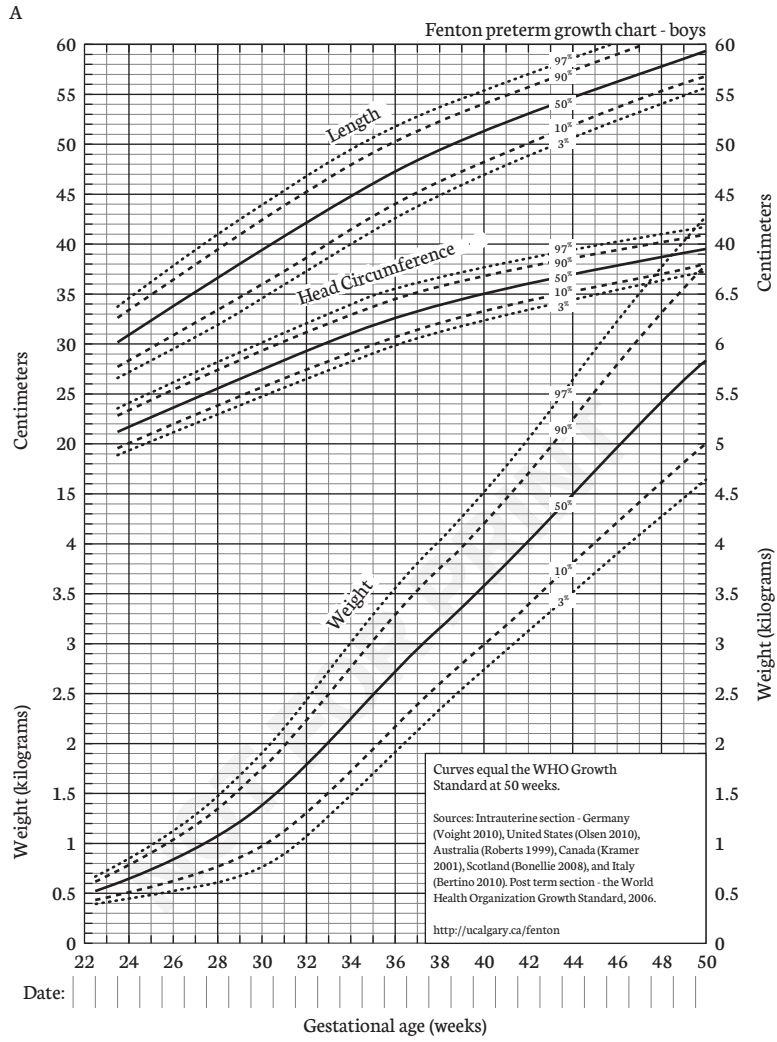
Reproduced with permission. Villar et al. *Lancet* 2014; 384: 857–968

*Charts are also available for biparietal diameter, femur length, adominal circumference, and occipitofrontal diameter. Available free from: https://intergrowth21.tghn.org/articles/intergrowth-21st-fetal-growth-standards/



Olsen BMI-for-age charts for intrauterine growth[2]

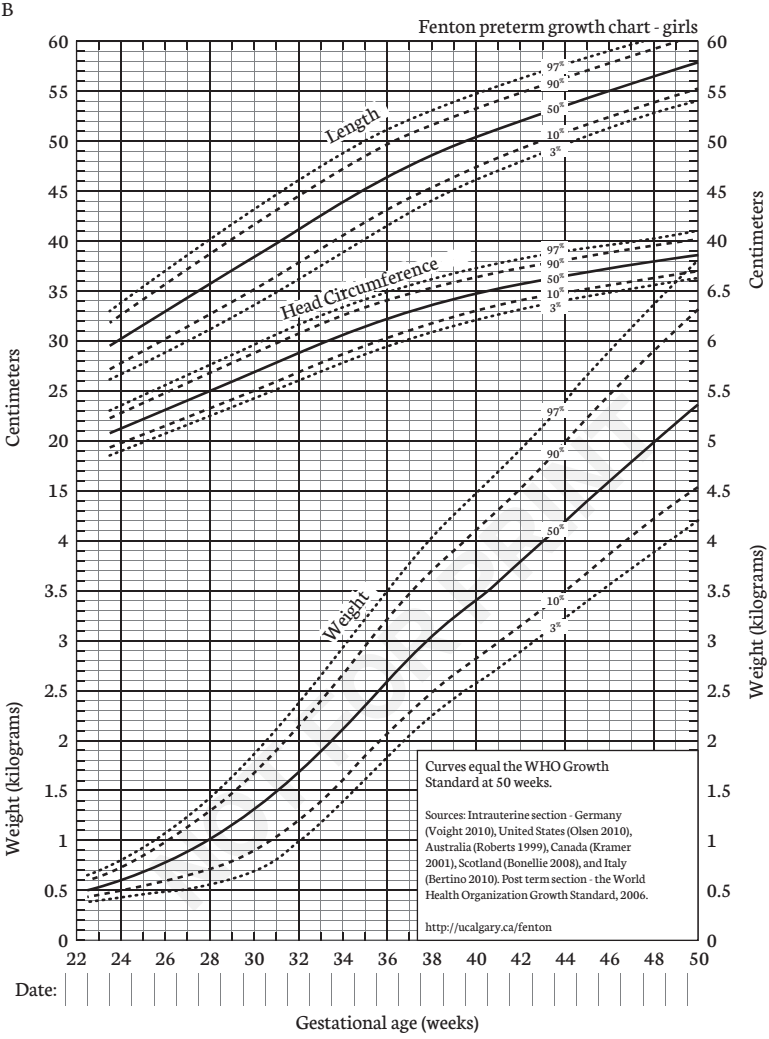
Reproduced with permission: Olsen et al. *Pediatrics* 2015; 135:e572–e581.



Fenton growth charts for preterm infants: A) Boys; B) Girls[3]

Reproduced with permission. Fenton TR, Kim JH. *BMC Pediatr* 2013;13:59.

B


Fenton preterm growth chart - girls
Length
Head Circumference
Weight
97%
90%
50%
10%
3%
Centimeters
Weight (kilograms)
Curves equal the WHO Growth Standard at 50 weeks.
Sources: Intrauterine section - Germany (Voight 2010), United States (Olsen 2010), Australia (Roberts 1999), Canada (Kramer 2001), Scotland (Bonellie 2008), and Italy (Bertino 2010). Post term section - the World Health Organization Growth Standard, 2006.
http://ucalgary.ca/fenton
Date:
Gestational age (weeks)

Additional sources for growth charts

World Health Organization Multicenter Growth Reference Study Group. WHO Child Growth Standards: Methods and Development. Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index for age: methods and development. 2006. Available at: http://www.who.int/childgrowth/standards/technical_report/en/index.html.

INTERnational Fetal Newborn Growth Consortium for the 21st Century. International postnatal growth standards for preterm infants. Available at: https://intergrowth21.tghn.org/articles/new-intergrowth-21st-international-postnatal-growth-standards-charts-available/.

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GROWTH TRAJECTORY AND ASSESSMENT, INFLUENCING FACTORS AND IMPACT OF EARLY NUTRITION provides an overview of physical growth during the first 1000 days - from conception to the age of two years, and the factors that influence the trajectory. The book discusses growth challenges that can occur, from compromised birth such as preterm, term small-for-gestational age and large-for-gestational age to growth deviations such as stunting and wasting, overweight and obesity in infancy and toddlerhood.

Healthcare professionals will come away with an understanding of growth assessment, the role of early nutrition in growth and the appropriate interventions to support healthy growth.

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