Abstract
The worldwide rate of premature birth is increasing. Survival has also improved, even for very preterm infants, meaning greater numbers of preterm infants surviving into later life. This has led to greater attention being focused on long-term outcomes. Recent interest in the Developmental Origins of Health and Disease has highlighted the importance of early life growth and nutritional exposures for chronic diseases such as cardiovascular disease, osteoporosis and type 2 diabetes. There is evidence linking preterm birth and poor growth in utero with worse long-term cognitive outcome, but also evidence to link more rapid growth in certain epochs of early life with adverse metabolic outcomes. The current data suggest that a diverse range of metabolic outcomes are affected by preterm birth, and that adult survivors may be more likely to develop certain chronic diseases. There are data to show that catch-up growth during the neonatal period and in infancy may affect these later outcomes, but studies are inconsistent in their findings. In addition, it is clear that lifestyle factors during childhood and adolescence have a major impact on metabolic disease that may be greater in magnitude to the effects of early growth and nutritional exposures.

Introduction
Dramatic improvements in neonatal care over the last 2–3 decades have resulted in increasing numbers of premature infants surviving longer term [1]. In economically advanced countries, survival at 24 weeks’ gestation (16 weeks premature) is now common. Even in less well-resourced countries, survival of very low birthweight (<1,500 g birthweight) infants is increasingly common. Throughout
the world, more than 15 million preterm births occur every year, and these rates look set to increase [1]. The reasons for an increase in the preterm birth rate are complex, but reflect changes to maternal age at first pregnancy, increased rates of multiple pregnancies (twins and higher-order multiples) and increasing use of assisted reproductive technologies such as in vitro fertilization. Preterm birth is associated with significant healthcare costs both in the short and longer term and is a major public health issue for all countries. The vast majority of preterm births (<37 weeks’ gestation) are also low birthweight (LBW, <2.5 kg birthweight) but the metabolic and cognitive costs of prematurity compared to LBW are different. This is important because nutritional strategies and their long-term impact need to be optimized to the individual: a ‘one size fits all’ approach to LBW babies will fail to optimize metabolic and cognitive outcomes. Providing the same ‘inputs’, and aiming for the same ‘outputs’ in a 2-kg appropriately grown preterm LBW infant compared to a 2-kg severely in utero growth-restricted (IUGR) term LBW infant will not optimize population outcomes.

Growth is a fundamental characteristic of all mammalian species and implies an increase in auxological measures (weight, length and head size or occipitofrontal circumference) along with changes in body composition. During the process of growth, there are changes to organ structure and function, and changes in response to endocrine stimuli. Adolescence is an important period particularly because of the impact of puberty and changing endocrine signals. Examining growth outcomes in early adulthood is also important. However, there are few studies of young adults born in the ‘modern’ era of neonatal medicine when use of antenatal steroids and artificial surfactant was widespread.

Developmental Origins of Health and Disease

Over recent years, the concept of the Developmental Origins of Health and Disease has gained increasing prominence in scientific study [2]. Animal studies in the 1950s demonstrated relationships between early patterns of growth (dependent on nutritional intake) and later size and metabolic outcomes [3]. However, the wider implication of these findings did not gain scientific prominence until the late 1980s and early 1990s when the translational relevance of the early growth impacts on later adult chronic disease (type 2 diabetes and cardiovascular disease) was documented in epidemiological studies. In a series of seminal papers, Barker showed clear relationships between size at birth and later chronic disease risk with term-born LBW infants having substantially increased risks [4]. Size at birth, i.e. LBW in this context, was used as an indicator of fetal growth. These studies predominantly explored outcomes in individuals born at term.
Studies led by the team of Lucas and Singhal extended these concepts, both confirming the associations in randomized controlled trials (RCTs) in preterm infants, but also highlighting the importance of growth patterns in early postnatal life on outcomes in adolescence [5–7]. Whilst data from Barker’s group suggested benefits to being larger in infancy, they concentrate on outcomes in late adult life, whereas Singhal identified that rapid growth in the immediate postnatal period may be the key factor associated with the greatest increase in later metabolic risk. Slower growth in utero may not result in later metabolic harm unless a period of rapid growth followed in the postnatal period.

The relevance to individuals born preterm is enormous, and currently underrecognized. Premature birth is frequently the end result of a compromised pregnancy, and many preterm infants show signs of IUGR when they are born [8, 9]. Premature birth may be induced because of maternal or fetal concerns, for example pregnancy-induced hypertension or preeclampsia. Preterm infants take time to tolerate enteral feeds and have to overcome many challenges including gastrointestinal immaturity that may be manifest as disordered motility, malabsorption or abnormal patterns of microbial colonization [10]. In addition, metabolic limitations such as hyperglycemia and technical challenges of providing parenteral nutrition (e.g. amino acid and fatty acid composition, mineral solubility, etc.) mean that most preterm infants fail to grow adequately over the initial few postnatal days and weeks [11]. Although growth that aims to match in utero references is widely promoted as an important aim of neonatal nutrition, there are no studies that define the optimal pattern of growth in preterm infants, particularly when Developmental Origins of Health and Disease thinking is considered. Nevertheless, most preterm infants are discharged from hospital with weights considerably below birth centiles. Numerous observational studies have shown strong relationships between early growth and later neurodevelopmental outcome [12]. These are supported by long-term follow-up of RCTs that show early nutrient intake to be a key modulator of later cognitive outcome [13].

**Catch-Up Growth, Growth Acceleration and Weight Gain**

The term ‘catch-up growth’ was first used by Prader and Tanner in the early 1960s to describe a period of rapid growth that followed a period of growth inhibition, and was usually referenced to linear growth (or height) [14]. The growth velocity in this period, linear growth in cm/week or weight gain in g/kg per day, will be above statistical norms for either age or developmental stage/maturity. The effect of this period of increased growth velocity is to take the in-
dividual back to their growth centile prior to the period of growth restriction. When considered from a preterm neonatal perspective, it becomes clear that it is difficult to define this process in a similar fashion. Fetal growth cannot be directly assessed: although in utero ultrasound may give an indication of change in auxological parameters, it is referenced to population norms that may not apply to the individual fetus. Many preterm deliveries are spontaneous with limited fetal monitoring. Given that there is a circular relationship between genes and the environment, it is similarly not possible to define whether growth is appropriate or restricted in terms of the infants’ ‘genetic potential’. Most often, catch-up growth is defined in terms of position on a growth chart, with upwards centile crossing or an increase in weight (or length) standard deviation score (SDS) taken to indicate catch-up. Even if the centile position at birth is regained, it may not be possible to state that full catch-up has occurred because birth-weight will also be a reflection of any degree of IUGR.

Whilst ‘catch-up growth’ has to involve ‘growth acceleration’, it may help to conceptualize a different scenario where growth acceleration results in the individual attaining a weight or length centile higher than appropriate (in homeostatic or physiological terms). An example of this can be seen in term infants who are formula rather than breast milk fed. Formula-fed infants exhibit greater early weight and length gains than those who are breast milk fed, possibly due to increased quantity or differences in milk quality. Formula milk contains higher levels of protein, so even at the same intake volume formula-fed infants may receive up to 50% greater protein intakes. This excess protein may stimulate IGF-1 and other endocrine processes resulting in faster weight gain, i.e. growth acceleration [15]. It is again important to reemphasize that growth implies both an increase in auxological measures and an appropriate change in body composition. Whilst weight gain is generally used to imply ‘growth’, similar patterns of weight gain can be seen in individuals who experience very different patterns of changes in body composition, i.e. fat and lean mass (LM) accretion. This is particularly important in adolescence where auxological measures and body mass index (BMI) may be insensitive measures of adiposity [16].

According to the above definitions, many preterm infants exhibit catch-up growth after their acute respiratory or gastrointestinal pathologies have resolved during their initial hospital stay. Although many preterm infants are discharged with weights less than the 10th centile, many also demonstrate catch-up in the immediate postdischarge period and during infancy. Catch-up growth in these periods can be accelerated by the use of enriched formula such as postdischarge formula, but the functional benefits of this approach remain unclear [17]. In the long-term, most preterm and LBW infants tend to demonstrate gradual catch-
up throughout infancy and childhood, so that very few remain outside the 95% confidence intervals of the population for weight and length in adolescence, although they are often still smaller than their peers.

It is clear that growth is not the same as weight gain, but weight is easy and precise to measure and tends to reflect changes in linear growth reasonably well especially after the first few postnatal weeks. Linear growth is extremely important, but is infrequently measured in clinical practice, and tends to be less precise. Alternate measures of linear growth such as ‘tibial’ length (or knee-heel length) can be extremely precise in experienced hands, but lack external validity as there are no references. Head growth is simple to measure and reflects brain size. However, many preterm infants’ heads become flattened during ex-utero life on the neonatal unit, and it is difficult to account for changing head shape on growth charts. Body composition is difficult to measure in routine clinical practice, and even in research settings most commonly used techniques (such as dual X-ray absorptiometry, DXA) involve many assumptions and may lack external validity especially when fat mass (FM) is considered. It is not surprising therefore, that studies of catch-up growth in preterm infants tend to use weight as the main indicator.

Adolescent Outcomes following Preterm Birth

Preterm birth is associated with an increased risk of a range of adverse growth, metabolic and cognitive outcomes. Whilst many individuals show catch-up growth, preterm born individuals tend to be slightly smaller in adolescence and early adulthood. This may not matter that much to the individual unless their size is well outside 95% confidence intervals, i.e. growth is not a functional outcome. Preterm-born adolescents show an increased incidence of decreased bone density, increased blood pressure (BP), insulin resistance, and abnormal adiposity, although studies demonstrate inconsistent effects [18]. Nevertheless, these are all considered surrogate markers for later life adult chronic diseases such as osteoporosis, hypertension, type 2 diabetes and obesity. Arguably the most important long-term outcome of preterm birth is impaired cognitive outcome. Global tests of developmental quotient (e.g. Bayley Scales of Infant Development) show that many preterm infants are significantly impaired in infancy, with longer-term studies demonstrating a changing pattern throughout childhood and adolescence [19]. Many individuals with moderate disability in infancy would not consider themselves as impaired, or experiencing a poor quality of life as adolescents. The extent to which cognitive or neurobehavioral outcomes are modifiable remains to be
determined, but there is evidence to suggest that nutrition plays a key role. Even though growth is dependent on many factors, there is strong evidence from experimental studies that nutrient quality and quantity determine patterns of growth [13]. Growth may be an important indicator of later outcomes, but growth per se is not the mechanism linking early nutrition and later metabolic or cognitive outcomes.

A recent large systematic review explored the association between preterm birth and later life metabolic outcomes. In a large review of over 17,000 preterm and 295,000 term-born adults, preterm birth was associated with significantly higher systolic and diastolic BP, and increased levels of low-density lipoprotein [20]. However, no significant differences were detected in insulin resistance (using fasting glucose or insulin levels). This may reflect populations studied, or the tests used, but is at variance with a recent systematic review from our group where we demonstrated decreased levels of insulin sensitivity throughout the life course in individuals born preterm [21]. Given the heterogeneity in population and technique, it was not possible to meta-analyze the data into an overall effect, but a series of well-characterized cohorts showed evidence of increased insulin resistance in individuals (including adolescents) born preterm. Necessarily, one of the problems with examining such long-term outcomes are the attritional losses over time, and the fact that adolescents or young adults reflect neonatal care from 20–30 years ago that may not be reflective of current populations and practices.

Although few studies also explored the associations between catch-up growth and adolescent outcomes, a large Dutch cohort study of preterm birth (average 29 weeks’ gestation) [22] showed a weak association between more rapid catch-up weight gain and insulin resistance in late adolescence (age 19 years). This relationship was significant for weight SDS at 3 months after term, but the study did not explore the precise timing of weight gain, i.e. whether it was predominantly before or after discharge. In a similar study, preterm born (average 32 weeks’ gestation) young adults (18–24 years) were compared to term matched controls [23]. Gain in weight-for-length prior to term was associated with adult %FM, and gain in weight-for-length between term and 3 months was associated with adult cholesterol and low-density lipoprotein. There was no significant association of birth-term, term-3 month or later epochs of weight gain with adult insulin sensitivity.

A recent series of papers from Belfort and colleagues have emphasized the association between early childhood growth and later metabolic and cognitive outcome. A follow-up study of 911 preterm-born children (6–8 years) examined the association of 1st-year weight gain, and showed that for each additional unit weight z score (SDS) increase, systolic BP was 0.7 mm Hg higher
and IQ score (measured using Wechsler Intelligence Scale for Children III) was 1.9 points higher [24]. The authors concluded that there appeared to be modest neurodevelopmental advantages of more rapid infant weight gain with only small BP-related effects. Whether similar effects will be seen in adolescence remains to be determined. In a further study, the same authors studied the effect of more rapid infant growth and IQ at 8 and 18 years of age [25]. At both outcome time points, the effects were similar. More rapid linear growth was associated with a decreased risk of low IQ, but a higher risk of overweight/obesity. Perhaps not surprisingly, more rapid BMI gain in all infant time intervals was associated with higher risk of overweight/obesity in later life, but there appeared to be a benefit of greater BMI gain between 4 and 12 months in terms of decreasing the risk of a low IQ. Taking these and other data together, it suggests there may be trade-offs that clinicians will need to assess [26]. Decreasing the chance of a low IQ may come with a metabolic cost. The trade-off will depend on the individual concerned. Rapid catch-up following IUGR may carry the greatest risk for adverse metabolic outcome. Very preterm infants may have greater potential for neurodevelopmental gain than those only born moderately preterm. Whilst there are no data to suggest that IUGR term-born infants have a neurodevelopmental benefit from rapid catch-up, it is clear that a ‘one size fits all’ approach for nutritional management cannot apply to all LBW infants.

Newcastle Preterm Birth Growth Study

We have recently explored the associations between catch-up growth in neonatal life, infancy and childhood, and adolescent outcomes in a well-characterized cohort of preterm infants originally recruited to one of 2 RCTs in the neonatal period [27]. In brief, >200 preterm LBW infants were recruited to either (a) a postdischarge study comparing standard to preterm formula (PTF) after discharge, that included a ‘crossover’ group who converted from PTF to standard formula at term, or (b) a study of PTF with varying protein density commencing in the predischarge period (around 32 weeks’ corrected age) and continuing after discharge until 12 weeks after term [28, 29]. Control groups of infants receiving breast milk were included. Infants were followed closely over the first 2 years of life with regular measures of growth (weight, length and occipitofrontal circumference) and body composition assessed using DXA to give measures of FM, LM and bone mineral mass. Auxological measures were converted to SDS using population growth references and weight gain calculated by subtraction to give a change in SDS over the period in question. Overall, the studies showed higher
rates of growth in infants on enriched formula that was not associated with excess FM deposition. In addition, careful measurement of intake volumes showed that infants on lower caloric densities upregulated intake volumes so that overall energy intakes between the groups (PTF or standard) were the same. This implies that any long-term effects observed in the study of the two main groups may be due to differences in protein intake (because protein:energy ratio differed) and not due to energy. Furthermore, it suggests complex relationships between growth and appetite control.

Children formula fed in the postdischarge trial were reviewed at 10 years of age and cognition assessed (92 out of 113 eligible = 80%). The entire cohort of children were further reviewed at 11–12 years of age (n = 153) and the assessment included growth, body composition (DXA), measures of insulin sensitivity (fasting glucose and insulin) and plasma lipid profile (102 consented to invasive blood testing). Data from these studies are in press or awaiting publication but show: (1) no long-term cognitive benefits of PTF versus standard formula; (2) an apparent cognitive disadvantage for infants who were converted from a PTF to a standard formula abruptly at term (crossover group); (3) positive associations between catch-up weight gain (increase in SDS) or head growth in infancy and specific domains of later cognition; (4) positive associations between catch-up weight gain before discharge and higher insulin sensitivity in adolescence; (5) negative associations between catch-up weight gain and insulin sensitivity immediately after discharge and in childhood; (6) positive associations between infant weight gain and adolescent bone mineral mass.

The data are in keeping with existing literature showing clear associations between early growth and later outcomes, but suggest that there may not be a metabolic disadvantage to more rapid weight gain when the entire predischarge period is considered. They support the notion that the postdischarge period is an important period for longer-term effects, suggesting that energy shortage (decrease in caloric intake) at a critical stage of rapid brain growth may have deleterious effects, but also that rapid weight gain after discharge may result in worse metabolic outcomes. This apparent paradox between the pre- and immediately postdischarge period may be explained by weight gain composition. In the predischarge period spanning several weeks, higher rates of weight gain may reflect better LM deposition and result in improved insulin sensitivity in later life. Alternately, higher weight gain may reflect more healthy infants (even though the effect persisted when adjusted for illness severity). Weight gain in the immediate postdischarge period (around 36 weeks to term-corrected age) spans a relatively short time, and more rapid gains are therefore likely to reflect differences in FM accretion.
Growth and Inference Causality

The mechanisms linking early growth and adolescent outcomes are complex, and are likely to be confounded and interacted by several factors, some of which will remain unknown, for example, specific genetic polymorphisms. Whilst there are clear associations with early growth, two of the key questions that remain are interlinked and are: (1) the extent to which growth is a reliable indicator of nutritional intake and status – what does the relationship between early catch-up growth and later metabolic effects imply in mechanistic terms? (2) The direction of the causal link – in observational studies there is a risk of reverse causation.

Whilst nutrition is the key determinant of growth, some of our previous studies have shown that nutrient intake differences can only explain around 50% of the variation in change in weight SDS [11]. It seems likely that there are other equally important factors shaping growth patterns that also affect the long-term outcomes of interest. In the widest sense, many of these factors are nutritional in nature, but may involve nutrient quality (e.g. breast milk components, fatty acids, or methyl donors) and effects on gene function such as epigenetic modification [30]. Additionally, whilst the data from our studies are in keeping with those from other groups, the precise direction of causality cannot be determined in observational studies, even where there is multiple adjustment for confounding factors. In our studies, adjusting for the severity of illness on later insulin resistance (by using mechanical ventilation as a proxy) or of parental factors on cognition (by adjusting for maternal educational level) did not change the significance or direction of the results. Nevertheless, such adjustment may not be adequate. It is quite likely that specific genetic differences, e.g. single-nucleotide polymorphisms, may have an effect on early LM accretion and later risk of insulin resistance. Statistical adjustment may make it appear that there is a direct link between LM and β-cell function, but in reality there may be a 3rd factor (genetic) that explains the association. It is important to recognize this, and be appropriately critical of long-term observational studies.

Conclusions: Mechanisms and Lifestyle Factors in Adolescence

A fuller discussion of the mechanisms linking catch-up growth with later outcomes in relation to LBW infants will be provided in other chapters. In brief, there are numerous mechanisms including structural differences, modifications to cellular ageing, and epigenetic effects [18]. Determining their precise roles will be extremely challenging especially given the life course nature of studies.
that attempt to link infant catch-up growth with adolescent metabolic outcomes. Finally, it is important to recognize the importance of other factors, particularly current lifestyle. Dramatic increases in obesity in adolescents reflect changing attitudes and behaviors to physical activity and dietary intake in the whole population. Differences in physical activity may be due to long-term neurobehavioral effects of preterm birth or LBW, or differences in muscle function, and may be confounded by infant nutrient exposures or current nutrient intakes (e.g. vitamin D). The ‘exposome’ of adolescents born LBW and preterm is extremely complex, especially when lifestyle factors are considered. It is clear that early growth is associated with adolescent outcomes, but the magnitude of the effect may be dwarfed by contemporary factors. This should be seen as encouraging, because lifestyle factors may be easier to modify or prevent than early life factors (e.g. poor fetal growth).

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References
