Effect of foetal and infant growth and body composition on respiratory outcomes in preterm-born children

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Abstract

Body composition and growth outcomes of preterm-born subjects have been studied by many researchers. In general, preterm-born children have lower height and weight especially in infancy. Despite showing potential for catch-up growth, they continue to lag behind their term counterparts in adolescence and adulthood. The various methods of studying body composition and the differing gestations and ages at which it is assessed may go some way to explaining the inconsistent results observed in different studies. In addition, there is a paucity of data on the effects of foetal and infant growth and of body composition on later respiratory outcomes. In largely term-born subjects, foetal growth and growth trajectories appear to have differential effects on later respiratory outcomes. Early weight gain in infancy appears to be associated with increased respiratory symptoms in childhood but catch-up growth in infancy appears to be associated with possible improved lung function status.

Keywords

Preterm, body composition, foetal growth, infant growth, lung function, respiratory.

Educational Aims

The reader will be able:

- To review the weight and height outcomes of preterm-born subjects.
- To report the effect of foetal and infant growth on later respiratory outcomes.
- To review the literature on the body composition outcomes of preterm-born subjects.
- To report the effect of body composition outcomes on later respiratory outcomes.

Future research directions

There is limited evidence on the effect of body composition and growth outcomes of preterm-born subjects on respiratory outcomes. Future research should focus not only on accurately reporting the longitudinal growth and body composition in preterm-born survivors but also the effect of both on future respiratory outcomes in childhood and beyond.

Introduction

The World Health Organisation has estimated 15 million babies are born prematurely every year [1]. In 2015, 91.7% of live births in England and Wales were delivered at full term i.e. ≥37 weeks' gestation, 7.6% of births were pre-term i.e. ≤ 37 weeks' gestation and gestational data was missing for 0.7% of births [2]. In the United States of America, the rate of pre-term birth was 9.57% in 2014 [3]. Thus, a large proportion of the population are born preterm every year. Studying the effect of prematurity on later growth and body composition outcomes is clearly important, as there may be an effect on other related outcomes such as metabolic disorders and also on the respiratory system [4]. Furthermore, the effect of catch-up growth in preterm-born subjects may have beneficial or adverse effects on respiratory outcomes.

There are many studies which report on somatic growth and body composition of preterm-born subjects. Discrepancies are seen in the results of these studies perhaps due to the fact that preterm-born subjects are born at a wide range of gestations, from 24 to 36 weeks' gestation, and suffer from a wide range of early neonatal problems which can impact adversely on nutrition and hence early growth [4]. With medical advances over time, including improved nutrition; long term body composition may improve. There is a paucity of results in preterm-born subjects linking body composition, foetal and infant growth with later respiratory outcomes. In this review we shall review the short and long term evidence of:-

1. The growth (height and weight) of preterm-born subjects.
2. Effect of foetal growth on later respiratory outcomes.
3. Effect of infant growth on later respiratory outcomes.
4. The body composition of preterm-born subjects.

5. The limited data on the links between body composition and lung function and respiratory symptoms in preterm-born subjects.

Growth outcomes

In this section growth is defined as body weight, height and body mass index (BMI). Preterm-born babies often have foetal growth failure due to maternal, foetal and placental reasons [5]. Similarly, especially in the extremely preterm group of ≤28 weeks' gestation, growth failure is common due to failure to establish satisfactory feeding due to a multitude of neonatal disorders [6]. A review on the growth of preterm-born children reported that there is growth failure in the early postnatal period [4]. Subsequently, there is often incomplete catch-up growth (which is defined differently in different studies) to predicted growth centiles with growth failure continuing into adolescence and adulthood leading to shorter and lighter adults [4].

The majority of studies have focused on the later growth outcomes of extremely/very preterm-born children and adults of ≤32 weeks' gestation or on preterm-born children and adults where preterm birth is defined as <37 weeks' gestation [7-21]. Poor growth in childhood (when growth is defined by height and/or weight measurements), is a common observation associated with premature birth [8-10, 12-14, 16-19, 22, 23]. By adulthood, some studies continue to report poor growth [7, 15, 20] but one study of preterm-born infants with a mean gestational age of 29.8 weeks reported that by 20 years of age, females catch-up in somatic growth but males do not when compared to a term control group with normal birth-weight [11]. In contrast, Gonzalez Stager et al. observed lower height more often in preterm-born adolescents than in term-born adolescents with a higher percentage of girls having a lower height but weight was not significantly different between the term and preterm groups [24]. Another study reported that preterm-born subjects with a mean gestational age of 27.4 weeks (SD 2.0) had achieved an average height consistent with their parents' heights [21]. The review by Doyle et al [25] of adult growth outcomes after extremely preterm birth of <28 weeks' gestation suggested that stature for most preterm-born subjects was within expected ranges despite both males and females being shorter; when compared to term-born controls.

For late preterm-born children, (different definitions are used but generally include part or all of the ranges between 32-36 weeks' gestation), poor growth has been reported in some studies [22, 23, 26, 27] but not all [28]. Santos et al. [23] reported that children born between 34 and 36 weeks' gestation were at an increased risk of stunting and were underweight at 12 and 24 months of age in comparison to term controls. Bocca-Tjeertes et al. [22] studied children born at 32-35$^{6/7}$ weeks' gestation noting that they were shorter and lighter during the first four years of life in comparison to term controls. In a large study of over 7,000 infants born at 34 to 42 weeks' gestation, there was an association between late prematurity (birth at 34-36 weeks' gestation) and increased risk of underweight status in the first year of life [27]. Boyle et al. in a recent study of the UK Millennium Cohort Study reported that height and weight were lower in the 32-33 and 34-36 weeks' gestation groups at 3 and 5 years of age when compared to the 39-41 weeks' gestation group [26]. In contrast, no significant differences were reported between the height and weight percentiles at a median age of 48 months for children born at 34-36 weeks' gestation when compared to children born at ≥39 weeks' gestation [28].

Thus, in general, preterm-born children including those born late preterm have lower height and weight especially in infancy. Despite showing potential for catch-up growth, they continue to lag behind their term counterparts in adolescence and adulthood.

Effect of foetal growth on later respiratory outcomes

Birth-weight is often used as a proxy for foetal growth. A small number of studies have reported the association of foetal growth with later respiratory outcomes in mainly term born children. The results are often contradictory, perhaps, as with the body composition results, due to different methods used in the different studies.

Turner et al reported a positive effect of an increase in crown-rump length (CRL) in the first trimester on the reduction of wheezing and diagnosis of asthma at 5 and 10 years of age in largely term-born children. In addition, at 10 years of age, an increase in CRL was associated with an increase in lung function [29, 30]. When growth patterns between the first and second trimester were investigated, growth acceleration was associated with an increased odds ratio of asthma; odds ratios for asthma were also increased in the persistently low growth group compared to the persistently high growth group at 10 years of age. In contrast, Sonnenschien-Van der Voort et al. did not find any significant effect of foetal growth patterns and later asthma symptoms when the Generation R study cohort, which contained both term- and preterm-born children, were followed up to 4 years' of age [31]. In the third study, by Pike et al., term-born children were followed up to 3 years of age. Foetal measurements were not significantly associated with early wheeze. However, decreased abdominal growth between 19 and 34 weeks' gestation led to an increased risk of atopic wheeze; but there was an increased risk of non-atopic wheeze with a decrease in head circumference growth in the early part of the second trimester [32]. We recently reported that accelerated foetal growth in preterm-born children was associated with increased wheeze in childhood or in pre-school and school aged children [33].

In conclusion, in largely term-born subjects, foetal growth and growth trajectories appear to have differential effects on later respiratory outcomes. Similar studies of contemporary preterm subjects for effect of foetal growth parameters on later respiratory outcomes are lacking [33].

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Effect of infant and childhood growth on later respiratory outcomes

The influence of birth-weight and catch-up growth on later respiratory outcomes has been addressed in a number of studies. In term-born children, we noted a positive association between birth-weight and lung function at 8-9 years of age but a lesser association at 14-17 years of age [34]. Lawlor et al. reported an association between birth-weight and adult lung function showing an association of 0.048 litre of FEV_1 for each kilogramme increase in birth-weight [35]. Weight gain in infancy and childhood has also been studied. We reported that catch-up growth in term-born children with intra-uterine growth restriction, compared to children who did not have catch-up growth, was associated with improvement in lung function although the improvement was not significant [36]. In contrast, in children born at ≥36 weeks' gestation, it was reported that rapid weight gain in the first 3 months of life was associated with an increased rate of doctor diagnosed asthma, and reduced lung function at 5 years of age [37]. This is in agreement with other studies that have reported weight gain in infancy is linked to childhood wheeze [31, 32] .

Peak weight velocity, (increased weight gain), in the first 2-3 years of life has been associated with asthma in childhood in mainly term-born children [38, 39]. At 15 years of age, lung function has been negatively associated with peak weight velocity in the first 2 years of age in term-born children [40]. Sonnenschein-van der Voort et al. studied growth patterns between birth and 10 years of age in children born at 35-42 weeks' gestation. Rapid weight growth between 3 and 7 years of age was associated with higher FVC and FEV_1 at age 15 years of age. In contrast, rapid weight growth between birth and 3 months of age was associated with lower FEV_1/FVC ratios at 8 and 15 years of age [41]. Turner et al. also reported an association between a higher rate of infant weight gain and a reduction in lung growth between 1 and 12 months of age [42]. In agreement, Lucas et al studied term-born infants and suggested that lower rates of growth in utero and gaining weight quickly in the first few weeks' of life were linked to reduced lung function at 5-14 weeks of age [43]. In contrast, Canoy et al studied adults at 31 years of age who were born full term and reported that there was a positive association between weight gain in the first year of life and later lung function [44]. Another study, which included preterm- and term-born subjects, linked lower birth-weight and weight gain in early childhood with reduced lung function in adulthood [45].

In a large meta-analysis studying the influence of preterm birth and infant weight gain on later childhood asthma, it was reported that both preterm birth and higher infant weight gain were linked to increased respiratory symptoms [46]. In a further meta-analysis, Den Dekker et al reported reductions in FEV_1/FVC as well as increased respiratory symptoms associated with infant weight gain but a higher FEV_1 was observed [47]. In our recent study, we reported that accelerated foetal growth in preterm-born children was associated with increased wheeze in pre-school and school-aged children. In addition, in children born at ≤32 weeks' gestation rapid weight gain in infancy was associated with increased wheeze in childhood. (OR 5.04 +/- 95% CI 3.36, 7.54) compared to term controls without rapid infant growth [33] (Figure 1).

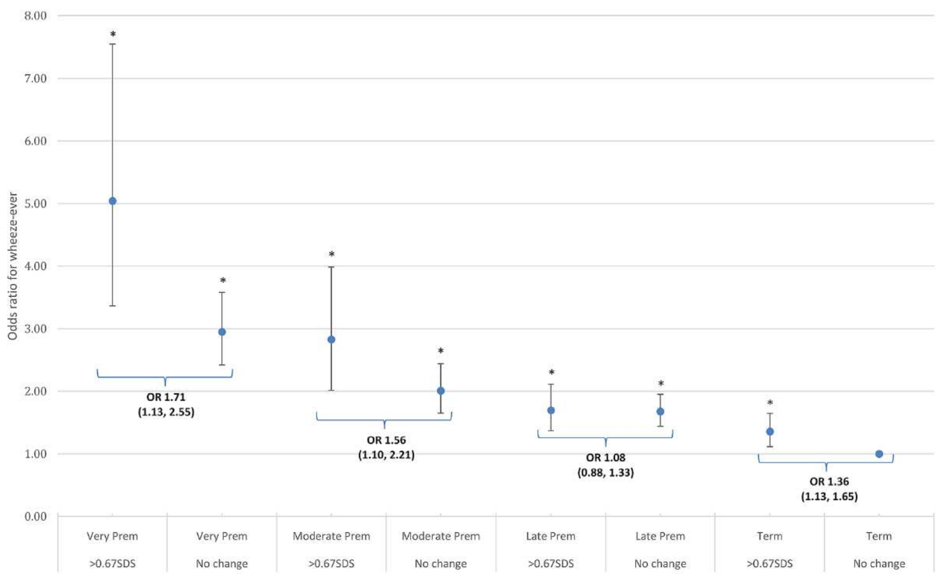


Figure 1: Graphical representation of interaction analysis (adjusted). All ORs for wheeze-ever are compared to the reference category of Term-born, no change in weight gain between birth and 9 months of age (*P<0.05 compared to reference category). Error bars represent 95% confidence intervals for ORs Reprinted with permission from Lowe at al. Pediatric Pulmonology 2017 with permission of John Wiley & Sons publications [33].

Loo et al. studied weight gain in the first 15 months of life in a cohort of term-born children and reported no significant associations between weight gain and wheeze in the first 3 years of life [48]. In contrast, Belfort et al. reported a higher risk of asthma at eight years of age with a faster gain in BMI in the first year of life in a cohort of preterm-born infants born with a birth-weight of ≤2.5kg [49]. The Born in Bradford cohort is a cohort of both preterm- and term-born children in whom wheezing symptoms or diagnosis of asthma were evaluated between 0-7 years of age. The children born with a low birth-weight had higher rate of wheezing symptoms or asthma. In addition, an initial low birth-weight followed by slow growth in the first three months of life followed by rapid growth up to 12 months of age was associated with increased risk of wheezing symptoms or asthma [50].

In summary, early weight gain in infancy appears to be associated with increased respiratory symptoms in childhood but catch-up growth in infancy appears to be associated with possible improved lung function. Although longitudinal studies, including infant lung function, are required to assess the underlying reasons for this discrepancy.

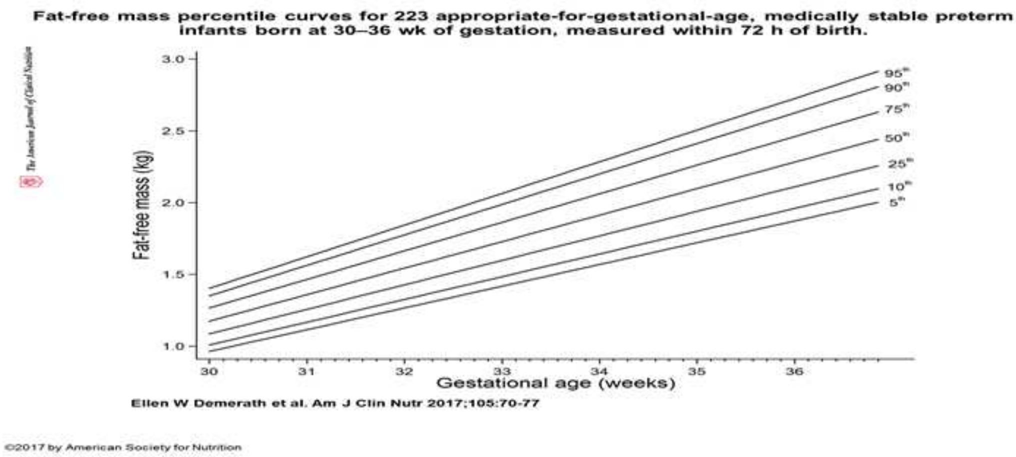
Body Composition Outcomes

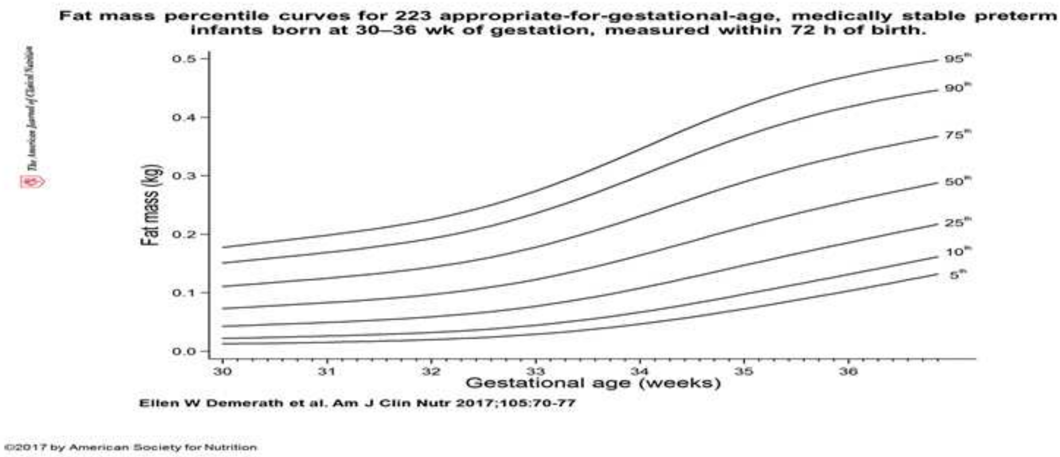
In this section, we shall review the body composition outcomes of preterm-born children. In view of the large number of preterm infants born each year, assessing their later growth and body composition is clearly important as there are possible links between altered body composition and future risk of metabolic, cardiovascular and possibly respiratory disease in later life [4, 51]. A recent study noted that the timing of catch-up growth may be important as catch-up growth in infancy was not linked to later metabolic outcome; in contrast, rapid weight gain after 1 year of age was linked to a higher fat mass and metabolic markers [52]. The majority of studies have focused on the later growth outcomes of extremely preterm-born children and adults or preterm-born children and adults where preterm birth is defined as <37 weeks' gestation. A number of studies also reported body composition [8, 13-15, 17, 19, 20, 53-61]. In recent years there has been increased interest in the longer term outcomes of infants born late preterm from 33-37 weeks' gestation. However, there is a paucity of data on the later growth and body composition outcomes of late preterm-born infants [22, 23, 26-28, 62].

Body composition in infancy

It has been recommended that preterm-born infants should have similar postnatal growth to the foetus [63], and body composition charts have been produced (Figure 2) [64]. Ahmad et al. been noted that "current postnatal care and nutritional support in preterm infants is still unable to match the in-utero environment for optimal growth and bone development" [65]. Besides nutritional factors, this may be due to neonatal disorders such as respiratory distress syndrome and poor feeding due to gut immaturity.

Figure 2 Reproduced with permission [64]





The review by Griffin and Cooke concluded that current research does not support the concern that preterm babies may have greater adiposity infancy than term babies [66]. Three studies noted that when compared to term-born infants or referenced standards, preterm-born infants have a higher percentage of body fat or fat mass around the time of discharge from hospital or at term corrected age [67-69]. A systematic review and meta-analysis of 733 infants reported that preterm-born infants at term equivalent age have similar fat mass but less lean tissue than term-born infants [70]. Tremblay et al reported that despite fat and lean mass percentages being similar at term equivalent age, preterm-born infants had more subcutaneous fat than term-born infants [71].

Body composition in late-preterm infants

Rapid increases in fat mass have been reported in late preterm-born infants between birth and term equivalent age [72]; another study at term equivalent age reported that late preterm infants had higher percentage of body fat compared to matched term-born infants [73]. In the latter study, most of the infants in both groups were breastfed. A recent systematic review compared the effect of breast and formula feeding on body composition in preterm-born infants at 36 weeks' corrected gestation. The authors concluded that formula feeding was associated with higher percentage of fat mass and fat free mass at 36 weeks' gestation compared to the breast-fed infants from birth [74]. It has been reported that late preterm-born infants have lower fat mass index and fat free mass index at birth, but by term equivalent age have higher fat mass index when compared to term-born infants [75]. Another study compared late preterm-born infants to term-born and extremely preterm infants. Late preterm infants had lower fat mass at 36 weeks' corrected age compared to the extremely preterm infants, but fat mass was similar to the extremely preterm and full-term infants by 3 months of corrected age [76].

Body composition in childhood and adults

Altered body composition has been reported by some studies in children and adults born preterm. One study reported lower lean and bone mass adjusted for height in preterm-born children aged 5-10 years of age with very low birth-weight (VLBW, <1.5kg) [53]. Gianni et al. reported that preterm-born children at term equivalent age had a lower fat free mass than term-born children. However, fat free mass index was lower in preterm-born males but not in females at five years of age [77]. In another study, 6-13 year old children with BPD had lower fat free mass when compared to term-born controls [78]. Zanini et al., reported that preterm-born children had lower measures of adiposity and lean body mass compared to term-born children at 6 years of age [79]. Scheurer et al. longitudinally studied preterm- and term-born children observing that body composition was similar at 3-4 years of age in both groups; despite differences at an earlier age [80]. In agreement, a study of young adults reported that lean body weight was not different when preterm-born subjects and term-born subjects were compared [81].

A lower lean body mass was also reported in a study of young adults born preterm compared to term controls [20]. In another study of 18-24 years old adults, those born preterm tended to have more total body fat, trunk fat mass and limb fat mass when compared to term controls [55]. Thomas et al. noted greater total and abdominal adipose tissue in preterm-born young adults aged 18-27 when compared to term-born controls [59]. Another study of young adults born with extremely low birth-weight (<1kg), noted lower lean mass for height, higher percentage body fat, but similar waist circumference when compared to normal birth-weight adults [82]. In contrast, two studies [56] [58] have reported lower fat mass preterm in school-aged children than in term-born children. In contrast, it has been reported that preterm-born adolescents have a higher fat mass compared to their term-born peers [24].

Mathai et al. reported increased abdominal adiposity and increased fat mass in adults born preterm. They also studied the children of the preterm-born parents. Despite the offspring being born at term, they also had increased abdominal adiposity suggesting an element of inheritance for body composition [83]. Another study of 5 years olds reported that preterm-born children have greater truncal adiposity despite there being no difference in total percentage fat mass when compared to term-born children [84]. In contrast, a study of 5-7 year preterm-born children reported there was no increase in fat mass or abdominal adiposity compared to term-born children [85]. In another study, preterm-born children had increased total body fat mass at term equivalent age but not increased intra-abdominal adipose tissue when compared to term-born infants [86].

Bone mineral density and bone mineral content

A review article noted that there are conflicting data on the effects of being born preterm on later bone mineral density [87]. Quintal et al. reported that at term equivalent age preterm-born children had lower bone mineral density and bone mineral content than term-born children. However, by 6 months of age there were no significant differences between the groups [88]. Fewtrell et al concluded that preterm children at 8-12 years have lower bone mass than term controls but the lower bone mineral content is appropriate for the preterm-born children’s body and bone size [14]. Breukhoven et al. concluded that premature birth (median gestation 32.2 weeks) is not linked with a lower bone mineral density in adults aged 18-24 years of age compared with term-born children [54]. A study of school age preterm children with and without BPD reported that both preterm groups were shorter than the term-born controls. Lean body mass was lower in the BPD group than in the term group and bone mineral content was lower in the BPD than in both of the other groups [13]. In another study, lower lumbar spinal bone mineral content and density were observed in 7 year old preterm-born children when compared to term-born children [17]. In the Helsinki Study of Very Low Birth-Weight Adults, bone mineral density was significantly lower in preterm-born adults aged 18-27 years with VLBW when compared to term-born controls [15]. In contrast, in the study by Erlandson et al., once results were adjusted there were no differences between the term and preterm groups for any of the bone mineral content results in adolescents [57]. In the study by Zamora et al., preterm-born girls aged 7-9 years had a lower areal bone mineral density at the hip and radial metaphysis but similar areal bone mineral density results at sites with predominantly cortical bone when compared to term-born controls [60]. Bowden at al. reported reduced bone mineral density in the hips at eight years of age in preterm-born children when compared to term-born controls [61]. In contrast, Stigson et al. reported that preterm-born children had a similar bone mass to term-born controls but lower lean mass and increased fat mass [89].

One study investigated bone structure and volumetric density by using peripheral quantitative computed tomography in preterm and term-born young adults. Smaller cross-sectional bone dimensions associated with lower bone strength index at the distal tibia were noted with a greater effect in males than in females [90]. In another study of preterm- and term-born 3-5 year olds, only the preterm-born boys had greater periosteal and endosteal circumferences with smaller cortical bone thickness and area; differences in current activity explained the differences [91]. The same group studied 7 year old term boys compared to preterm-born, (≤34 weeks' gestation), and late preterm-born boys, (>34 and ≤37 weeks' gestation). They did not report any significant differences in lean body mass or percentage body fat between preterm or late preterm-born children when compared to children born at term. However, the preterm boys had lower bone size and mass than term-born boys and late preterm boys had lower bone mass than term-born boys at several bone sites. Despite the differences in bone mass and size physical activity did not differ between the preterm and term groups [62].

The studies of body composition outcomes of preterm-born children report conflicting results. The different methods used to study body composition, and the differing gestations and ages at the time of study may go some way in explaining the different results observed in the different studies.

Linking body composition to respiratory outcomes

The linking of body composition with respiratory outcomes for preterm-born subjects is poorly studied. In one of the few studies, Bott et al. studied preterm-born children at 4-8 years of age who had BPD in infancy. They reported that 18/52 (35%) of the children were undernourished (Figure 3). Fat mass, fat free mass and z-score of bone mineral density were significantly lower in these 18 children when compared to the rest. Interestingly, girls were more frequently undernourished than boys. In addition, they reported that under nutrition at 2 years of age is linked with hyperinflation of the airways at 4-8 years of age [8]. Clearly, body composition may be another factor for the low lung function observed in preterm-born subjects [92, 93]

Figure 3

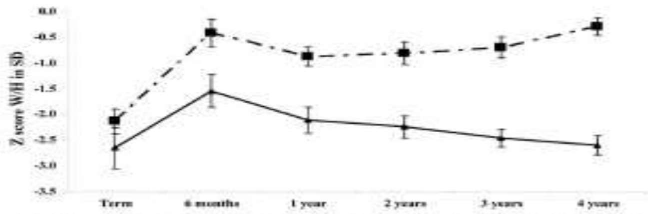


Figure 1. Differences in *Z* scores of weight/height (SD) between undernourished (▲) and normally nourished (■) children from term to 4 y (n = 52). Time effect: $p < 0.0001$; group effect: $p < 0.0001$; interaction: $p < 0.0001$.

Conclusion

In summary there is conflicting information regarding the later growth and body composition of preterm-born children and adults compared to term-born groups. This may be, due to the fact that the preterm-born subjects are born at a range of gestational ages, undergo a wide range of medical interventions and are born over a number of decades during which medical treatment has changed. In largely term-born subjects, foetal growth and growth trajectories appear to have differential effects on later respiratory outcomes. There is paucity of results in preterm-born subjects linking body composition, infant and foetal growth and later respiratory outcomes. The optimal way to prevent later deficits in body composition and to optimise growth needs further investigation. The linkages between later health outcomes including respiratory outcomes and growth and body composition outcomes also needs further study.

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