Prematurity and reduced body fatness at 8–12 y of age

Mary S Fewtrell, Alan Lucas, Tim J Cole, and Jonathan CK Wells

ABSTRACT
Background: Increasing evidence suggests that body composition, an important factor influencing morbidity and mortality in adult life, might be programmed by early growth and nutrition. Children born preterm remain shorter and lighter than their term-born peers during childhood, but it is unclear whether the size difference is associated with altered body composition.

Objective: We tested the hypothesis that both fat mass (FM) and fat-free mass (FFM) are proportionately lower in children born preterm than in children born at term.

Design: A total of 497 children born preterm and 95 children born at term were studied at 8–12 y of age. Body composition was determined with the use of skinfold thicknesses and dual-energy X-ray absorptiometry (in 200 preterm and 95 term children). FM and FFM were normalized for height to give fat mass index (FMI) and fat-free mass index (FFMI), respectively.

Results: Children born preterm were significantly lighter than those born at term and had lower FM and FFM. However, FMI was significantly lower in preterm children, whereas FFMI was not. FMI was also significantly lower in boys than in girls and in children with higher activity levels. Additional data available for the preterm group showed no association between birth weight, gestational age, or neonatal diet and later FMI or FFMI.

Conclusions: The smaller size of children born preterm than of children born at term is associated with lower FM but not FFM when normalized for height. We hypothesize that this could result in a reduction in the risk of obesity and related diseases during adult life.

KEY WORDS Preterm infant, term infant, body composition, fatness, programming

INTRODUCTION
Increasing evidence suggests that infant growth and nutrition play a role in the development of obesity. For example, breastfeeding (1–5), delayed introduction of solid foods (6), and lower protein intake at age 10 mo (7) are associated with reduced fatness in later life. Most research on the cause and consequences of obesity is based on proxy measures of fatness such as weight or body mass index. However, more sophisticated methods are now available to examine separately the development of fat mass (FM) and lean body mass and their relative contributions to later outcome.

Several studies showed that growth and body composition in preterm infants during the neonatal period are influenced by their diet (8–13), and children born preterm are known to remain shorter and lighter than children born at term throughout childhood and adolescence (14–22). Whether their smaller size is associated with alterations in body composition is less clear, yet it could arguably be more important for their later health. Peralta-Carcelen et al (15) reported that adolescents born with birth weight < 1000 g attained lower growth measurements than adolescents born at term but had similar relative body composition measured with the use of dual-energy X-ray absorptiometry (DXA).

One of the difficulties in comparing body-composition measurements between groups of children, particularly when the groups differ in weight or height, is that of expressing the measurements in an appropriate manner, that is, normalizing them for body size. The use of weight for normalization, eg, as percentage fat or lean, precludes individual consideration of FM and lean mass because one is the inverse of the other. This issue was recently discussed by Wells et al (23). One proposed solution is to normalize FM and fat-free mass (FFM) separately by adjusting them for height. In its simplest form, as proposed by Van Itallie et al (24), both FM and FFM are divided by height2. However, this approach could produce indexes of FM and FFM that remain correlated with height. By regressing log FM or log FFM on log height, it is possible to determine the appropriate power by which height should be raised to produce indexes that are uncorrelated with height.

We previously reported smaller body size at 8–12 y of age in children born preterm than in children born at term (22). The aim of the current analysis was to compare body-composition measurements between the 2 cohorts to test the hypothesis that, as previously reported (15), the smaller size of the preterm children was associated with lower FM and FFM.

SUBJECTS AND METHODS
A total of 497 children who had been born preterm and participated in a randomized trial of diet during the neonatal period were recruited for a follow-up study between 8.8 and 12.7 y of age. All had a birth weight < 1850 g (x ± SD: 1377 ± 304 g; range: 622–1847 g) and were born at < 37 wk gestation (x: 31 ± 3 wk; range: 25–36 wk). Details of the original trial and dietary

1 From the Medical Research Council Childhood Nutrition Research Centre (MSF, AL, and JCKW) and the Centre for Paediatric Epidemiology and Biostatistics (TJC), Institute of Child Health, London.
2 Supported by the Medical Research Council (United Kingdom).
3 Reprints not available. Address correspondence to MS Fewtrell, MRC Childhood Nutrition Research Centre, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, United Kingdom. E-mail: m.fewtrell@ich.ucl.ac.uk. Received July 10, 2003. Accepted for publication January 12, 2004.
randomizations are given elsewhere (11). For the current follow-up, children were seen either at a local hospital or at their family practitioner’s office by 1 of 2 investigators. Weight was recorded with the use of digital scales, and height was recorded to the nearest 0.1 cm with the use of a portable stadiometer. Midupper arm circumference (MUAC) and waist circumference were recorded with the use of a paper measuring tape. Biceps, triceps, subscapular, and suprailiac skinfold thicknesses were measured in duplicate by 1 of 2 investigators with the use of Holtain calipers (Holtain Ltd, Crymnych, Wales). Pubertal status was self-assessed with the use of pictures of the Tanner stages for breast (female) or genital (male) development (25) and was coded as prepubertal (Tanner stage = 1) or pubertal (Tanner stage ≥ 2) for analysis in view of the small number of children in stage 3 and above. A simple assessment of the child’s activity level was made by asking the parents to rate their child compared with his or her peers (less, the same, more, or much more).

A whole-body bone densitometry scan (Hologic QDR 1000W; Hologic Inc, Bedford, MA) was performed on 200 of the children while they wore light indoor clothing. This scan provides measurements for bone mineral content (BMC), FM, and FFM. Previously reported precision values for DXA are <1% for lean mass and <2% for FM in adults (26).

Ninety-five children of the same age range but born at term were recruited as a reference group for the current follow-up study from schools in Cambridge, and they underwent the same investigations as the preterm cohort, including DXA scans. Ethical approval for the study was obtained from the Dunn Nutrition Unit committee and from the research ethics committees of the 5 original participating centers. Written informed consent was obtained from the parents of all participating children, as was assent from each child.

**Calculation of body fat mass and fat-free mass**

Body FM and FFM were calculated from skinfold thicknesses with the use of 2 published equations applicable to the age range of the children. The equations of Slaughter et al (27) for percentage body fat for children with triceps and subscapular skinfold thicknesses < 35 mm are as follows: for boys, percentage body fat = 1.21(sum of 2 skinfold thicknesses) − 0.008(sum of 2 skinfold thicknesses²) − 1.7; for girls, percentage body fat = 1.33(sum of 2 skinfold thicknesses) − 0.013(sum of 2 skinfold thicknesses²) − 2.5. The equations for percentage of body fat for children with triceps and subscapular skinfold thicknesses ≥ 35 mm are as follows: for boys, percentage body fat = 0.783(sum of 2 skinfold thicknesses) − 1.7; for girls, percentage body fat = 0.546(sum of 2 skinfold thicknesses) + 9.7.

The equations of Deurenberg et al (28) were used to calculate predicted body density (in kg/L) as follows: for boys, body density = 1.1133 − 0.0561 × (log sum of 4 skinfold thicknesses) + 1.7(age × 10⁻³); for girls, body density = 1.1187 − 0.063 × (log sum of 4 skinfold thicknesses) + 1.9(age × 10⁻³). Percentage body fat was then calculated as follows: percentage fat = ([c1/D] − c2), where D = body density, and c1 and c2 are coefficients varying with age and sex (16).

FM (in kg) was calculated with the use of the percentage fat measurement obtained from the whole-body DXA scan, and the weight was measured with the use of digital scales. Calculations were performed separately with and without BMC included in the FFM component. For each of the 3 methods (Slaughter, Deurenberg, and DXA), FM and FFM were normalized for height as suggested by Van Itallie et al (24) to give fat mass index (FMI) and fat-free mass index (FFMI) as follows: FMI = FM/height², and FFMI = FFM/height².

To determine the extent to which FMI and FFMI were correlated with height and to find the appropriate power by which to raise height to produce indexes uncorrelated with height, log-log regression analyses were performed (with the use of natural logarithms). The regression slope corresponds to the power (P) by which height should be raised to calculate an index (FM/height² or FFM/height²) that is uncorrelated with height.

Indexes of body composition were also calculated with the use of MUAC (29) as follows: total midupper arm area (TUA) = MUAC²/(4 × π), arm muscle area (AMA) = [MUAC − (triceps × π)]²/(4 × π), and arm fat area (AFA) = TUA − AMA.

**Statistics**

Body-composition variables were compared between preterm and term cohorts with the use of Student's t test. Multiple regression analyses were performed if variables were significantly different between cohorts to adjust for potential confounders (age, sex, pubertal status, and level of physical activity).

The association between birth weight SD score (calculated with the use of 1990 UK standards), gestation, neonatal diet (coded as banked breast milk, term infant formula, or preterm formula) and proportion of human milk, and childhood body composition was examined with the use of stepwise multiple regression models. Analyses were performed with the use of SPSS version 10.0 (SPSS Inc, Chicago).

**RESULTS**

Anthropometric and body-composition variables calculated with the use of the different methods are given in Table 1 according to cohort. Despite a significantly higher mean age, children from the preterm cohort were significantly lighter than the term children and had significantly lower body mass index, as well as biceps, triceps, and suprailiac skinfold thicknesses. Waist circumference was lower, although not significantly so, in the preterm cohort.

Percentage fat, FM, and FMI from both skinfold thickness equations and from DXA were significantly lower in the preterm cohort. FFM from DXA and from Deurenberg equations and FFMI from DXA were also significantly lower, whereas FFM from Slaughter equations and FFMI by both skinfold equations were not significantly different between cohorts.

Log-log plots were used to determine the appropriate power by which height should be raised to give a modified FMI and FFMI uncorrelated with height. The value of power for FM was 4.5 for all 3 methods, whereas power for FM was 2.5 for Slaughter equations and DXA (2.4 with BMC subtracted), and 2.7 for Deurenberg equations. The modified FMI and FFMI according to cohort are shown in Table 2. Preterm children had significantly lower modified FMI by all 3 methods, but modified FFMI did not differ between groups.

AFA was also significantly lower in the preterm cohort, whereas AMA was not different in the 2 groups. The ratio of triceps to subscapular skinfold thickness was significantly lower in children born preterm, which suggests greater truncal fat deposition relative to arm fat deposition in this group.

Modified FMI was adjusted for potential confounding factors (Table 3). For all 3 methods, FMI was significantly higher in...
TABLE 1
Anthropometric and body-composition data according to cohort

<table>
<thead>
<tr>
<th></th>
<th>Preterm (n = 497)</th>
<th>Term (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>11.2 ± 0.89</td>
<td>10.6 ± 0.86</td>
</tr>
<tr>
<td>Boys [% (n)]</td>
<td>51 ± 256</td>
<td>55 ± 52</td>
</tr>
<tr>
<td>Attained puberty</td>
<td>30 ± 151</td>
<td>23 ± 22</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>35.4 ± 8.5</td>
<td>37.6 ± 8.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>141.6 ± 9.0</td>
<td>142.9 ± 7.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.5 ± 2.8</td>
<td>18.2 ± 3.0</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>60.8 ± 7.2</td>
<td>62.3 ± 7.6</td>
</tr>
</tbody>
</table>

Skinfold thickness (mm)

- Biceps: 7.2 ± 3.3
- Triceps: 11.6 ± 4.2
- Subscapular: 8.4 ± 4.2
- Suprailiac: 10.5 ± 6.4
- MUAC (cm): 21.5 ± 2.7
- TUA (cm²): 37.5 ± 10.1
- AFA (cm²): 12.9 ± 6.3
- AMA (cm²): 252.5 ± 56.6

Slaughter equations
- Percentage fat (%): 18.4 ± 5.9
- Fat mass (kg): 6.84 ± 3.70
- Fat-free mass (kg): 28.6 ± 5.5
- FMI (kg/m²): 3.34 ± 1.62
- FFMI (kg/m²): 14.1 ± 1.5

Deurenberg equations
- Percentage fat (%): 18.8 ± 5.2
- Fat mass (kg): 6.88 ± 3.36
- Fat-free mass (kg): 28.3 ± 5.5
- FMI (kg/m²): 3.38 ± 1.46
- FFMI (kg/m²): 14.1 ± 1.5

DXA equations
- Percentage fat (%): 20.1 ± 8.3
- Fat mass (kg): 7.14 ± 4.32
- Fat-free mass (kg): 26.4 ± 4.9
- BMC (g): 1061 ± 254
- FFMI (kg/m²): 3.59 ± 1.99
- FFMI (kg/m²): 13.5 ± 1.4

1 MUAC, midupper arm circumference; TUA, total midupper arm area; AFA, arm fat area; AMA, arm muscle area; FMI, fat mass index; FFMI, fat-free mass index; DXA, dual-energy X-ray absorptiometry; BMC, bone mineral content.

2 ± SD (all such values).

3,5,7,8 Significantly different from term: 3P ≤ 0.001, 5P < 0.05, 7P < 0.005, 8P < 0.01.

4 Tanner stage ≥ 2.

5,6,8 Nearly significantly different from term: 5P = 0.06, 6P = 0.05.

6 P = 0.02.

7 P = 0.02, 8P < 0.001.

8 Including BMC.

TABLE 2
Modified fat mass index (FMI) and fat-free mass index (FFMI) according to cohort

<table>
<thead>
<tr>
<th></th>
<th>Preterm</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slaughter equations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMI (kg/m²)</td>
<td>1.39 ± 0.63</td>
<td>1.59 ± 0.74</td>
</tr>
<tr>
<td>FFMI (kg/m²)</td>
<td>11.9 ± 1.2</td>
<td>12.0 ± 1.1</td>
</tr>
<tr>
<td>Deurenberg equations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMI (kg/m²)</td>
<td>1.42 ± 0.57</td>
<td>1.58 ± 0.66</td>
</tr>
<tr>
<td>FFMI (kg/m²)</td>
<td>11.0 ± 1.1</td>
<td>11.2 ± 1.0</td>
</tr>
<tr>
<td>DXA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMI (kg/m²)</td>
<td>1.56 ± 0.82</td>
<td>1.81 ± 0.89</td>
</tr>
<tr>
<td>FFMI (kg/m²)</td>
<td>11.4 ± 1.6</td>
<td>11.6 ± 1.0</td>
</tr>
<tr>
<td>FFMI (kg/m²)</td>
<td>11.0 ± 1.4</td>
<td>11.2 ± 1.0</td>
</tr>
</tbody>
</table>

1 All values are ± SD. DXA, dual-energy X-ray absorptiometry.

2–4 Significantly different from term: 2P = 0.02, 3P = 0.03, 4P = 0.01.

5 With bone mineral content subtracted from lean mass.

DISCUSSION

Children born preterm are lighter during mid-childhood than are children born at term. This finding is consistent with previous reports (14–22). However, contrary to our hypothesis, our results suggest that the lower weight of children born preterm is associated with lower FM rather than lower FFMI when these measurements are expressed as modified indexes, normalized for height.

Peralta-Carcelen et al (15) reported similar percentages of fat, lean tissue, and bone measured with the use of DXA in adolescents born with very low birth weight than in adolescents born at term. Although the children in that study were of lower birth weight and were older when studied, the apparent difference in conclusion between that study and ours could also reflect the different approaches used to normalize body-composition data. In our study, FM and FFMI were individually normalized for height to produce indexes that are independent of each other, whereas in the previous study, FM and FFMI were expressed as a

TABLE 3
Factors predicting modified fat mass index (FMI)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Coefficient</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slaughter FMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>0.14</td>
<td>2.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Activity rating</td>
<td>−0.12</td>
<td>−3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Term compared with preterm</td>
<td>0.16</td>
<td>2.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Tanner stage ≥ 2</td>
<td>0.2</td>
<td>3.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (y)</td>
<td>−0.07</td>
<td>−2.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Deurenberg FMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>0.15</td>
<td>3.0</td>
<td>0.003</td>
</tr>
<tr>
<td>Activity rating</td>
<td>−0.11</td>
<td>−3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tanner stage ≥ 2</td>
<td>0.20</td>
<td>3.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>−0.12</td>
<td>3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DXA FMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>0.44</td>
<td>4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Activity rating</td>
<td>−0.14</td>
<td>−2.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Term compared with preterm</td>
<td>0.22</td>
<td>2.2</td>
<td>0.03</td>
</tr>
</tbody>
</table>

1 Stepwise multiple regression models with FMI as dependent variable and age (y), sex (male = 1, female = 2), pubertal status (prepubertal = 1, pubertal = 2), activity rating (lowest = 1, highest = 4), and preterm or term (preterm = 1, term = 2) as independent variables. P value for inclusion = 0.05. DXA, dual-energy X-ray absorptiometry.
percentage of body weight so that each proportion was still dependent on the other. In fact, calculation of FMI and FFMI from the data provided in the previous study gives very similar findings to ours, with a greater deficit in FMI than FFMI in the preterm group. Ultimately, the relative value of different methods of normalizing body-composition data needs to be established by assessing their relation with clinical outcome measures or events.

Our findings of lower modified FMI in the preterm children remained after adjustment for potential confounding factors for 2 of the 3 methods. As expected, other factors were also influential. Girls had greater FM than did boys, and children who had already reached puberty had greater FM than did those who had not. However, there was no evidence that the effect of prematurity on body composition differed in boys and girls. Importantly, the child’s reported activity level compared with that of his or her peers was also influential, with higher FMIs in less active children. Although this rating of activity level might be regarded as crude, Sallis et al (30) reported significant correlations between self-rated activity level and each of the following: body mass index, ratio of HDL cholesterol to LDL cholesterol, and fitness in children.

Our study was not designed to compare different methods for assessing body composition. However, it is interesting that the results for FM produced by DXA were higher than those produced with the use of skinfold thickness equations in our study, as previously reported by others (31). Nevertheless, regardless of the relative accuracy of the techniques, the findings obtained through the use of DXA in our study were the same as findings obtained from a larger number of the same cohort through the use of skinfold thicknesses and MUAC and support the validity of the results reported.

Several studies showed that growth and body composition in preterm infants during the neonatal period can be influenced by either their diet or the degree of growth restriction experienced in utero. For example, infants fed preterm formula were reported to have greater FM deposition and bone mass gain than infants fed fortified human milk (8), whereas preterm infants born appropriate for gestational age had higher percentage fat at term than infants born small for gestational age (9). Cooke et al (10) also reported greater lean and bone mass measured with the use of DXA in preterm boys at 12 mo after term than in preterm girls. Our own randomized trials of nutrition during the neonatal period in preterm infants, including the cohort studied here, demonstrated marked diet-related differences in weight, length, and head circumference gain during the first weeks and months of life (11–13). However, longer-term follow-up of these infants suggests that, although on average they remain smaller than their term peers, dietary effects on growth do not persist into childhood (22, 32). Nevertheless, the apparent absence of early dietary effects on growth or body composition during childhood does not exclude the possibility of later emergence of programmed effects during adolescence or beyond, as reported in both primates and humans. For example, Lewis et al (33) found that baboons overfed for a brief period during infancy became obese during adolescence after a period of normal weight during childhood.

We found no effect of size for gestational age at birth on either FM or FMI in later childhood in our preterm cohort. In contrast, studies of infants born growth retarded at term have suggested an association between poor fetal growth and reduced lean mass rather than reduced FM at follow-up. For example, Hediger et al (34) reported on a cohort of 4431 children aged 2–47 mo from the United States. With the use of skinfold thicknesses and MUAC-derived upper arm fat and muscle indexes, they found that infants with a birth weight below the 10th centile had a persistent deficit in upper arm muscle area, with no significant difference in fat area compared with infants born appropriate for gestational age.

Our finding that children born preterm have a lower proportion of fat than do children born at term might reflect the timing of the development of FM during fetal life. We found no relation between gestational age and later FM within the preterm cohort, all of whom were born before 37 wk of completed gestation. This finding would suggest that whatever is responsible for the later effect on FM in these infants must occur at (or operate until) a relatively late stage in gestation. Fat accretion occurs predominantly during the last trimester. It is possible that disruption of the normal pattern of in utero fat deposition in preterm infants has a long-term effect on subsequent fat gain. This disruption could potentially be mediated by alterations in leptin physiology as we have previously suggested (35). Low FM during a critical period early in postnatal life could result in up-regulation of hypothalamic leptin receptors and an increased sensitivity to leptin later in life.

The clinical significance of our findings is unclear. It is tempting to assume that having a low FMI would be beneficial in terms of later health outcomes. However, the preterm group also had a lower ratio of triceps to subscapular skinfold thickness that would be consistent with relatively greater truncal fat deposition. We are currently undertaking a further follow-up of this cohort in early adult life, with assessment of body composition together with measurement of markers for later cardiovascular disease, including plasma lipids and insulin resistance. This follow-up will enable us to establish the predictive value of different methods of normalizing body-composition data for later outcome. In addition, it will allow us to examine whether altered body composition persists into adult life, to look for the emergence of effects related to early nutrition, and to determine whether any such effects are likely to have beneficial or adverse consequences for later health.

We thank the children and their parents for participating in the study and Sarah Jones for help with data collection.

MF, JW, and AL were involved in designing the study and interpreting the data. MF was also involved in data collection and prepared the manuscript. TC provided advice on the statistical analysis of the data. All the authors reviewed the manuscript, provided suggestions for revision, and approved the final version submitted for publication. None of the authors had any conflicts of interest.

REFERENCES