Preterm Birth and Body Composition at Term Equivalent Age: A Systematic Review and Meta-analysis

abstract

BACKGROUND AND OBJECTIVE: Infants born preterm are significantly lighter and shorter on reaching term equivalent age (TEA) than those born at term, but the relation with body composition is less clear. We conducted a systematic review to assess the body composition at TEA of infants born preterm.

METHODS: The databases MEDLINE, Embase, CINAHL, HMIC, “Web of Science,” and “CSA Conference Papers Index” were searched between 1947 and June 2011, with selective citation and reference searching. Included studies had to have directly compared measures of body composition at TEA in preterm infants and infants born full-term. Data on body composition, anthropometry, and birth details were extracted from each article.

RESULTS: Eight studies (733 infants) fulfilled the inclusion criteria. Mean gestational age and weight at birth were 30.0 weeks and 1.18 kg in the preterm group and 39.6 weeks and 3.41 kg in the term group, respectively. Meta-analysis showed that the preterm infants had a greater percentage total body fat at TEA than those born full-term (mean difference, 3%; \( P = .03 \)), less fat mass (mean difference, 50 g; \( P = .03 \)), and much less fat-free mass (mean difference, 460 g; \( P < .0001 \)).

CONCLUSIONS: The body composition at TEA of infants born preterm is different than that of infants born at term. Preterm infants have less lean tissue but more similar fat mass. There is a need to determine whether improved nutritional management can enhance lean tissue acquisition, which indicates a need for measures of body composition in addition to routine anthropometry. Pediatrics 2012;130:e640–e649

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KEY WORDS infant, premature, body composition, adiposity, leanness, nutrition assessment, nutrition requirements, infant nutrition, growth

ABBREVIATIONS

ADP—air-displacement plethysmography

ATV—adipose tissue volume

CI—confidence interval

DXA—dual energy x-ray absorptiometry

FFM—fat-free mass

FM—fat mass

SD—Standard Deviation

%TBF—total body fat as a percentage of body weight

TBW—total body water

TEA—term equivalent age

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(Continued on last page)
A goal for the nutritional care of infants born preterm is to achieve rates of growth similar to those of the fetus in utero at the equivalent gestation.1 This growth needs to be similar both qualitatively and quantitatively, so that both the size and body composition of the preterm infant at term equivalent age (TEA) are similar to those of infants born at full-term. In practice, intrauterine growth rates are a difficult target to achieve and “extraterine growth restriction” is common.2 However, while there is good evidence that preterm infants do not currently achieve the size of term infants at TEA,3 it is less clear whether the pattern of tissue growth is similar to that of infants born at term. It is recognized that body size and composition in early life relate to the risk of noncommunicable diseases, such as coronary heart disease, in later life; therefore, understanding the body composition at TEA of preterm infants is important.4-6 The composition of weight gain in low birth weight infants varies in response to nutrient intake,7 and an objective for improved nutritional management could be the acquisition of an appropriate body composition in preterm infants by TEA.

Studies exploring the relationship between preterm birth and body composition at TEA have had mixed findings. In part, this may be explained by the use of a variety of methods for measuring neonatal body composition by different investigators, including isotope dilution, dual energy x-ray absorptiometry (DXA), air-displacement plethysmography (ADP), and MRI. All of these methods are indirect and rely on a range of assumptions, not all of which have been appropriately validated for this population.8,9 No single method has been shown to give a more reliable estimate of body composition than another. Care has to be taken to recognize that for preterm infants, intrauterine growth itself may have been constrained. Infants born preterm may experience different patterns of growth in utero before delivery compared with infants born at term.10 Thus, any comparison between full-term infants with those born preterm at TEA may be comparing groups that were different at the equivalent intrauterine age. Hence, the assumption that a comparison is being made between ex utero tissue accretion (in the preterm infants) with in utero tissue accretion (in the full-term group) may not be justified.

There is a need to better define the relationship between preterm birth and body composition at TEA. We therefore set out to systematically review the available literature and conduct a meta-analysis to determine if differences in body composition could be identified between infants born preterm upon reaching TEA and those born at term with regard to fat-free mass (FFM), fat mass (FM), and total body fat as a percentage of body weight (%TBF).

METHODS

Search terms, inclusion criteria, and methods of analysis were documented in a protocol in advance of the start of the review; the details follow.

Eligibility Criteria

Types of Studies

All types of studies were considered for review and no language restrictions were imposed.

Types of Participants

Only studies that made direct comparisons between premature infants (born at <37 weeks’ gestation) at TEA (37–42 weeks’ postmenstrual age) and infants born at term using the same method were selected for review. Studies where the preterm population was assessed at <37 weeks’ postmenstrual age were excluded.

Studies assessing the effects of modified feeds were excluded, as were studies looking specifically at infants born small or large for gestational age, infants of diabetic mothers, or infants with specific conditions (eg, chronic lung disease, congenital heart disease).

Types of Methods

To be included, studies had to have measured a defined component of body composition (FFM, FM, and %TBF) by using a recognized technique for measuring neonatal body composition.8,9 Studies in which estimates of body composition were based on a derivation with formulas using anthropometry, skin folds, or bioelectrical impedance (“doubly indirect” methods) were excluded.

Types of Outcome Measures

The primary outcome measures for the study were the differences in components of body composition (FM, FFM, and %TBF) in preterm infants at TEA compared with those born full-term. Secondary outcome measures were differences in weight, length, and head circumference in preterm infants at TEA compared with those born full-term.

Searches and Information Sources

An all language literature search was carried out using the key words and search strategy detailed in Table 1. The electronic databases MEDLINE (1947 to present), Embase (1947 to present), CINAHL (1981 to present), and Health Management Information Consortium were searched by using OvidSP (Wolters Kluwer, www.ovid.com). The last search was run on June 1, 2011. Conference abstracts and other citations were identified by searching the web sites “Web of Science” (wok.mimas.ac.uk) and CSA Conference Papers Index (www.csa.com) using the same search strategy outlined in Table 1, adapted for use in the web interface. Handsearching of conference proceedings was also...
circumference at the time of study. With numerical data, both mean and standard deviation (SD) values were extracted. For included studies where data for FM, FFM, and %TBF were not published in the original article, authors were contacted and asked if they could provide this information. While 5 responded, only 1 author was able to provide additional information (E. Olhager, personal communication, September 29, 2010).

Assessment of Heterogeneity and Risk of Bias for the Included Studies

Given the variety of different methods used to assess body composition in infants, the main factors likely to cause bias and imprecision for the included studies were the precision and validity of the methods used. The cited references regarding the method and validation work used in each study were therefore examined to help inform the assessment of bias and precision. In addition, the postnatal age in days of the full-term infants at the time of study was anticipated to cause a degree of bias in assessing body composition due to the rapid changes in total body water (TBW) over the first 2 weeks after birth.\textsuperscript{11,12}

It was anticipated that, due to the variation in methodology between studies, there would be considerable heterogeneity. The decision was taken to only include studies that directly compared both full-term and preterm infants at TEA using the same method to allow for this.

Data Synthesis and Analysis

Meta-analysis was performed looking at the difference in means between preterm infants at TEA and infants born full-term using the random-effects model. Mean differences with 95% confidence intervals (CIs) were calculated for each outcome measure. Analysis was carried out by using the software Review Manager v5.1.\textsuperscript{13}

Heterogeneity across studies for each outcome measure was assessed according to the method of Higgins et al, using the $I^2$ measure to describe the percentage of the variability in effect due to heterogeneity.\textsuperscript{14} In cases where SDs were not given, these were calculated from CIs if available or from the median and the range as described by Hozo et al.\textsuperscript{15}

While DXA and ADP provide data on the fat component of body composition as FM, MRI techniques give adipose tissue volume (ATV). Therefore, for MRI studies where ATV was provided rather than FM, ATV was converted to FM by using a conversion factor of 0.66 kg of FM for every 1 L of ATV.\textsuperscript{16}

RESULTS

Study Selection

A flowchart of the review process is shown in Fig 1. Initial searches identified 954 articles and abstracts for review. After removal of duplicates, there were 658 articles that were screened for eligibility; 616 were discarded as it was clear from their abstracts or titles that they did not meet the criteria. Common reasons for rejection included the assessment of body composition in preterm infants only without term controls, the use of doubly indirect methods for assessing body composition, focus on a specific disease population, the comparison of novel feeds, and reviews concerning nutritional management. The remaining 42 citations were selected for full-text review, of which 34 were excluded for the reasons given in Fig 1. Eight studies met the inclusion criteria and were included in the systematic review.

Study Characteristics

The 8 included studies, together with their characteristics, participants, and methods, are shown in Table 2.

### TABLE 1

<table>
<thead>
<tr>
<th>Number</th>
<th>Search Term</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>exp Body Composition/</td>
</tr>
<tr>
<td>2</td>
<td>(body adj composition).mp.</td>
</tr>
<tr>
<td>3</td>
<td>fat*.mp.</td>
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<td>4</td>
<td>thin*.mp.</td>
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<tr>
<td>5</td>
<td>adipos*.mp.</td>
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<tr>
<td>6</td>
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</tr>
<tr>
<td>7</td>
<td>(total adj body).mp.</td>
</tr>
<tr>
<td>8</td>
<td>exp Infant, Newborn/ or neonate*.mp. or newborn*.mp.</td>
</tr>
<tr>
<td>9</td>
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</tr>
<tr>
<td>10</td>
<td>(fat adj mass).mp.</td>
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<td>12</td>
<td>adiposity.mp.</td>
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<tr>
<td>13</td>
<td>(fat adj free).mp.</td>
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<tr>
<td>14</td>
<td>lean.mp</td>
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<tr>
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<td>prematur*.mp.</td>
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<td>18</td>
<td>9 or 10 or 11 or 12 or 13 or 14</td>
</tr>
<tr>
<td>19</td>
<td>1 or 2 or 3 or 4 or 5 or 6 or 7</td>
</tr>
<tr>
<td>20</td>
<td>8 and 17 and 18 and 19</td>
</tr>
</tbody>
</table>

Searches were performed by using OvidSp, where “mp.” represents a multipurpose search across the fields of title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, and drug manufacturer.
The included studies had a total study population of 733 and were undertaken in neonatal units in Europe, Australia, and North America. The preterm group at TEA totaled 388, with a mean gestational age at birth of 30.0 (SD 2.6) weeks and a mean birth weight of 1.18 (SD 0.33) kg. The full-term group totaled 345, with a mean gestational age at birth of 39.6 (SD 1.3) weeks and a mean birth weight of 3.41 (SD 0.60) kg.

Body composition in the preterm group was assessed at a mean of 39.5 (SD 1.5) weeks’ postmenstrual age, and the full-term group was assessed at a mean of 39.8 (SD 1.4) weeks’ postmenstrual age. There was thus no significant difference in the postmenstrual age at assessment between the 2 groups (P = .10). For Ahmad et al, only the term and preterm 23- to 28-week groups were included in the meta-analysis, as the other subgroups (29- to 32-week and 33- to 36-week gestations) had not been assessed at TEA (mean ages at assessment, 35.3 and 35.6 weeks, respectively). Forest plots for the meta-analyses of body composition and anthropometry are shown in Figs 2 and 3, respectively, and the results are summarized in Table 3 and discussed later. Results shown are given as mean (95% CI, P value).

**Risk of Study Bias**

Investigation into the relative accuracy and validity of the 3 methods (DXA, ADP, and MRI) used across the included studies revealed that while they all had similar precision (represented by coefficients of variation ranging from 3% to 8% in published validation studies), they differed in their ability to accurately estimate FM and %TBF in relation to the reference standards or techniques used in their validation. Validation work referenced by the studies included in the review that used DXA showed that it tended to overestimate FM or %TBF by 12% to 30%, while in the methodologic references for studies using ADP, this figure was lower, with ADP differing from the reference standard by 0.05%.
to 0.6% in either direction. Studies referenced for method validation work in neonatal MRI suggested it tended to overestimate %TBF by ∼6%.

The decision to look at the differences between body composition in the study populations rather than the absolute values should, in theory, allow them to be considered and analyzed together. However, in view of this variation in method accuracy, an overall meta-analysis for each outcome was performed, and subgroup analysis of studies using the same methods was carried out to aid interpretation of results.

Specific data regarding the chronological age of the full-term infants at the time of study was only available in 3 of the 8 studies. However, with the exception of one study, in which the full-term infants were studied at a mean age of 16 days, the full-term infants were studied within the first week of life. TBW is relatively high at birth and then falls rapidly over the first week of life, meaning that the full-term infants are likely to have had relatively higher TBW

**FIGURE 2**
Forest plots of meta-analyses of differences in (A) %TBF, (B) FM, and (C) FFM between infants born preterm at TEA and those born full-term.
compared with the preterm infants, who were measured when much older (∼2 months of age). This potentially could have influenced measures of FFM in the full-term group, although it is likely that any effect would have been minimal, as the change in TBW as a proportion of body weight over the first days of life is in the order of 2%.36

Primary Outcomes: Body Composition

**Percentage Total Body Fat at TEA in Preterm Versus Full-term Infants**

Seven of the 8 studies assessed %TBF (n = 672; 366 preterm and 306 full-term infants). Meta-analysis of all 7 showed that infants born preterm had significantly greater %TBF at TEA by 3.06% (95% CI 0.25%–5.88%, P = .03; see Forest plot in Fig 2A) compared with infants born at full-term, with significant heterogeneity (I² = 93%, P < .001). For the methodology subgroups, the heterogeneity was less and it was only in the ADP subgroup that preterm infants at TEA had significantly greater %TBF compared with infants born full-term.

**Fat Mass at TEA in Preterm Versus Full-term Infants**

Five of the included studies contained data for FM (n = 297, 140 preterm and 157 full-term infants). Meta-analysis of these 5 studies showed that preterm infants had significantly less FM at TEA compared with those born full-term. The mean difference was 50 g (95% CI 10–90 g, P = .02; see Forest plot in Fig 2B). There was no evidence of heterogeneity (I² = 0%). For the

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**TABLE 3** Summary of Results of Meta-analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies Included in the Meta-analysis (No. of Patients)</th>
<th>Mean Effect of Preterm Birth on Body Composition at TEA Compared With Infants Born Full-term (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>%TBF</td>
<td>7 (672)</td>
<td>Increased in preterm infants by 3.0% (0.25%–5.88%)</td>
<td>.03</td>
</tr>
<tr>
<td>FM</td>
<td>5 (297)</td>
<td>Decreased in preterm infants by 50 g (10–90 g)</td>
<td>.02</td>
</tr>
<tr>
<td>FFM</td>
<td>3 (137)</td>
<td>Decreased in preterm infants by 480 g (270–540 g)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Weight</td>
<td>7 (577)</td>
<td>Decreased in preterm infants by 590 g (440–750 g)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Length</td>
<td>4 (383)</td>
<td>Decreased in preterm infants by 3.7 cm (2.8–4.6 cm)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Head circumference</td>
<td>5 (450)</td>
<td>Decreased in preterm infants by 1 cm (0.5–1.5 cm)</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>
methodology sub-groups, neither the DXA nor MRI subgroups showed a significant difference in FM between preterm at TEA and full-term born infants.

Fat-Free Mass at TEA in Preterm Versus Full-term Infants

In the 3 studies that reported data on FFM (n = 137, 50 preterm and 87 full-term infants), meta-analysis showed that preterm infants at TEA had significantly less FFM than full-term infants, with a mean difference of 460 g (95% CI 0.27–0.64, P < .001; see Forest plot in Fig 2C). As for FM, the heterogeneity (I2 = 57%) was not significant (P = .10). The findings were consistent for the methodology subgroups, with both MRI and DXA showing significantly less FFM in the preterm infants at TEA.

Secondary Outcomes: Anthropometry

Weight at TEA in Preterm Versus Full-term Infants

Seven studies reported data for weight at TEA (n = 577, with 319 preterm and 258 full-term infants). Meta-analysis showed that preterm infants at TEA age were significantly lighter than full-term infants by a mean of 590 g (95% CI 440–750 g, P < .001; see Forest plot in Fig 3A).

Length at TEA in Preterm Versus Full-term Infants

Meta-analysis of the 4 studies that had comparative figures for length (n = 383, with 209 preterm and 174 full-term) showed that preterm infants at TEA were significantly shorter by a mean of 3.71 cm (95% CI 2.81–4.60 cm, P < .001; see Forest plot in Fig 3B).

Head Circumference at TEA in Preterm Versus Full-term Infants

Head circumference was assessed in both groups at TEA in 5 studies (n = 450, with 247 preterm and 203 full-term). Meta-analysis showed that head circumference at TEA was significantly less in the preterm group by a mean of 1.03 cm compared with infants born full-term (95% CI 0.54–1.52 cm, P < .001; see Forest plot in Fig 3C).

DISCUSSION

This systematic review and meta-analysis shows that infants born preterm have a different body composition at TEA compared with infants born at term. They have substantially less FFM with a more similar FM. They have a greater %TBF that in large part is explained by the lesser FFM rather than an increase in FM per se. This analysis supports the findings from other studies that infants born preterm are significantly shorter and lighter and have a smaller head circumference at TEA than those born at full-term. If infants born at full-term are used as the reference against which to compare intrauterine growth and tissue accretion, then infants born preterm have not achieved this reference for either growth or body composition by the time they reach TEA.

This analysis was limited by the fact there were few studies in which the body composition of preterm infants at TEA was compared with those born full-term directly. For these studies, the only consistently reported measure of body composition was %TFBF, with few studies reporting separate figures for FM or FFM. The heterogeneity in measures of composition was high, particularly for %TFBF, which could in part be attributed to differences in the methods used, the timing of measurements, and the relative ages of the 2 populations in each study.

Nevertheless, the meta-analyses for FM and FFM indicate consistency in the pattern of body composition seen in preterm infants at TEA. The differences between the groups for FM were modest, ∼50 g, with lack of consistency across methodology subgroups. By contrast, the difference for FFM was much greater, ∼480 g, and was consistent across all methodology subgroups. From this, it can be concluded that the significant difference in body weight between preterm infants at TEA and infants born full-term, a mean of 590 g in this study, can be substantially attributed to a difference in FFM. The appearance is of a significant constraint on the acquisition of lean tissue but not on FM. However, without detailed information on the body composition of the preterm infants around the time of birth, it is not possible to be sure the extent to which this difference in FFM can be attributed to poorer intrauterine growth or a limitation in postnatal accretion of lean tissue. The relative deficit in FFM in the preterm group might in part be attributed to their being significantly shorter at TEA, but in itself this does not seem adequate to explain the magnitude of the difference.

An important consideration is the extent to which differences in the pattern of body composition seen in preterm infants at TEA have implications for their health in later life. Previous work has shown that a low birth weight increases the risk of obesity and noncommunicable disease in adulthood, and preterm birth itself has been associated with an increased risk of hypertension, cardiovascular disease, and type 2 diabetes. Alterations in body composition in terms of both the relative amounts of fat compared to lean tissue and the distribution of fat are likely to disrupt normal patterns of growth and have also been shown to affect metabolic function later in life. The study by Uthaya et al included in this review demonstrated that preterm infants at TEA have altered distribution of fat, with
increased intra-abdominal adiposity compared with those born at term. In addition, the pattern of growth seen in this study, with decreased weight, relatively greater adiposity, but, most important, a deficit in lean tissue, has been observed in full-term Indian babies, where it has been associated with an increased risk of type 2 diabetes and relative adiposity in later life. The mechanisms responsible for the difference in body composition of preterm infants and the relative paucity of lean tissue are likely to be multifactorial, with altered body composition representing the final common pathway for a range of exposures that modulate the preferred partitioning of nutrients to lean tissue growth. These include the availability of an appropriate pattern of nutrients for growth and other factors that influence the handling or availability of nutrients, such as concurrent illness (including infection and lung disease), hormonal influences (including the use of postnatal corticosteroids), and the transition from intravenous to enteral sources of nutrition. The usual nutrient acquisition of the fetus during the last trimester of pregnancy is exceptional for any period of life, with marked lean tissue and adipose deposition together with the acquisition of hepatic reserves of micronutrients, such as iron, zinc, and copper. The shift from nutrient delivery through the umbilical vein to an enteral intake through an immature gastrointestinal tract presents a large challenge, as has been highlighted in several studies in this population. Carlson and Ziegler found that the energy and protein intakes of preterm infants fell short of those estimated to be needed to replicate in utero growth. By using recommended intakes as a reference, Embleton et al demonstrated cumulative deficits in protein and energy intakes in preterm infants during the first weeks of life that were directly related to subsequent postnatal growth restriction. These findings are particularly pertinent to the results presented here, as deficits in energy and/or protein can lead to impaired lean tissue accretion. However, a recent study by Rochow et al showed that while increased energy and protein intakes improved the growth of preterm infants, there was no significant effect on body composition at TEA compared with historic preterm controls. Therefore, additional attention has to be given to the quality of the protein provided in the diet and the relative adequacy in terms of dietary indispensable amino acids. In turn, the needs for total nitrogen and the ability of the immature infant to generate conditionally essential amino acids in sufficient amounts must also be considered. For example, we have been interested in how the fetus/infant generates adequate amounts of glycine, serine, and cysteine to meet the substantial needs for net tissue deposition, metabolic regulation and integration. Using urinary S-oxoproline as a marker for glycine status in preterm infants suggests that it may be limiting in this population. Given the complexity of nutritional needs and their interactions, it seems likely that no single nutrient alone constrains the acquisition of lean tissue in preterm infants but rather a combination of interrelating factors, which includes specific nutrient availability. To date, no studies have looked in detail at the relationship between the provision of all macronutrients and micronutrients in the first weeks after preterm birth and subsequent growth and body composition at TEA.

CONCLUSIONS

By carrying out a meta-analysis of the relevant work in this area, this review has enabled a summary description of the relationship between preterm birth and body composition at TEA with more clarity and confidence. Preterm infants at TEA are lighter and shorter and have smaller head circumferences but, in addition, have a significant relative deficit in lean tissue. This has immediate implications in terms of their functional reserve and susceptibility to ill health and has far-reaching consequences for their health and risk of noncommunicable disease in later life. It is likely that this pattern of body composition is in part a consequence of the nutrition that these infants receive while in hospital. More work is needed looking at the supply of individual nutrients in this vulnerable group and how this relates to their growth and body composition at TEA. Importantly, this study also demonstrates that standard anthropometry alone is inadequate to fully assess the growth and nutritional status of preterm infants, suggesting a role for measures of body composition as a routine part of growth monitoring. There is a need to be clearer on the extent to which these differences in body composition at TEA should be attributed to altered intrauterine growth or postnatal tissue accretion. However, reliable assessment of body composition during this vulnerable period of rapid change is challenging, with a lack of practical and robust methodologies. The development and validation of improved methods for reliably assessing body composition in preterm infants early in life are priorities for understanding and improving their nutritional care.

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