Effects of breast-feeding compared with formula-feeding on preterm infant body composition: a systematic review and meta-analysis

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Abstract
We conducted a systematic review and meta-analysis to compare the effect of breast-feeding and formula-feeding on body composition of preterm infants. We searched the literature using PubMed, Cochrane Central Library Issue, Ovid (Medline), Embase and other resources such as Google Scholar, electronic databases and bibliographies of relevant articles; two reviewers collected and extracted data independently. All the authors assessed risk of bias independently using the Newcastle–Ottawa Scale (NOS). A fixed-effects meta-analysis was undertaken with RevMan 5 software (The Cochrane Collaboration) using the inverse variance method ($P \geq 0.05; \chi^2$ test). In contrast, a random-effects meta-analysis was carried out. Altogether, 630 articles were identified using search strategy, and the references within retrieved articles were also assessed. A total of six studies were included in this systematic review. In formula-fed infants, fat mass was higher at term (mean difference 0.24 (95% CI 0.17, 0.31) kg), fat-free mass was higher at 36 weeks of gestational (mean difference 0.12 (95% CI 0.04, 0.21) kg) and the percentage of fat mass was higher at 36 weeks of gestation (mean difference 3.70 (95% CI 1.81, 5.59) kg) compared with breast-fed infants. Compared with breast-feeding, formula-feeding is associated with altered body composition from birth to term in preterm infants. The effects of formula-feeding on preterm infant body composition from term to 12-month corrected age are inconclusive in our study. Well-designed studies are required in the future to explore the effects of formula-feeding compared with breast-feeding.

Key words: Breast-feeding: Formula-feeding: Preterm infants: Body composition

To achieve optimal growth, preterm infants need better nutrition in the neonatal period than any other time of their life because of decreased intra-uterine nutrient deposition(1). The American Academy of Pediatrics recommends that breast milk should be the preferred feeding for all infants. Formula milk is recommended when human milk supply is inadequate or the mother is unable to breast-feed(2). Meanwhile, preterm infants often require additional supervisions and support systems compared with term infants, because their buccal coordination and swallowing mechanisms are not fully matured(3). In addition, despite lower weight and shorter length than term infants upon discharge, preterm infants have been found to show a catch-up growth and abnormal adiposity at term corrected age, which indicates a potential risk factor for CVD(4,5). Therefore, it is essential to monitor growth and body composition changes continuously in relation to different nutrition interventions, because growth pattern and body composition appear to have a long-term effect on health outcomes(6).

It is quite clear that a period of rapid growth would be likely to have negative effects on long-term health outcomes(7), and unbalanced catch-up growth of fat mass (FM) could attribute to this association. At the same time, two types of rapid catch-up growth in preterm infants exist(8): one is paralleled by an increase in ‘predominantly FM’ and the other by ‘predominantly fat-free mass’ (FFM). Moreover, evidence suggests that FFM and FM can also provide precise determinations of body composition or measurement(9). Therefore, important implications can be obtained by measuring FM and FFM.

Despite the critical inter-relationship between early nutrition, growth, development, and subsequent health, a few data are

Abbreviations: FM, fat mass; FFM, fat-free mass.

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available on changes of body composition in preterm infants during the 1st year of life. In addition, systematic reviews that determine the effect of formula milk feeding compared with maternal breast milk feeding on rate of growth and developmental outcomes in preterm or low birth weight infants have been inconclusive, because no data from randomised trials of formula milk v. maternal breast milk for feeding preterm or low birth weight infants could be obtained[10]. Meanwhile, the study of Fewtrell et al.[13] suggested that breast-feeding or high-sn-2 infant formula has no significant effect on bone mass in the long term.

The purpose of our study was to assess the effects of breast-feeding v. formula-feeding on body composition by collecting all the evidence available from cohort studies comparing the effects of breast-feeding v. formula-feeding on preterm infant body composition.

Methods

Protocol and registration

Our systematic review was registered at http://www.crd.york.ac.uk/PROSPERO/, with the registration number CRD42015023335.

Eligibility criteria

(1) The participants were preterm infants (≤37 weeks of gestation at birth and/or 2500 g) without congenital malformations or complications affecting body composition.

(2) The types of exposure were breast-feeding (exclusive or predominant) and formula-feeding (exclusive or predominant). Broadly, formula milk can be considered as follows: (i) ‘term’ formulae, designed for term infants providing 280–293 kJ/100 ml (67–70 kcal/100 ml); (ii) ‘pre-term’ formulae, designed to provide nutrient intakes to match intra-uterine accretion rates with energy enrichment (about 335 kJ/100 ml (80 kcal/100 ml)), variably protein and mineral enrichment[12]. The effects of breast-feeding and formula-feeding on body composition were measured at the same time points.

(3) The outcomes were FM (kg), FFM (kg) and the percentage of FM. We excluded studies in which body composition was measured by skinfold thickness because of its poor ability to predict body composition[13].

(4) The types of studies were cohort studies; no language restrictions were placed. Review articles and commentaries were excluded.

Information sources

This systematic review was designed and carried out according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[14]. This included electronic searches of databases such as PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Cochrane Central Library Issue, Ovidmedline), Embase and other resources (such as Google Scholar). All databases were searched from their earliest records to May 2015 and were updated in August 2015.

Search

Subject terms, keywords and truncation symbol were used in the search strategy. The search method was adjusted in accordance with each database, using a combination of key words such as ‘(Premature Birth)’ OR ‘(Infant, Premature)’ OR ‘(Labor, Premature)’ AND ‘(Infant formulas)’ OR ‘(artificial formula)’ OR ‘(breast feeding)’ OR ‘(human milk)’) AND ‘(body composition)’ OR ‘(Body Fat Distribution)’), as well as Medical Subject headings (MeSH) terms; for example, ‘(Breast feeding)’ AND ‘(Infant formula)’ AND ‘(Infant premature)’ AND ‘(Body composition)’. The search strategy details are given in the online Supplementary material. References of eligible articles and previous reviews were manually searched for studies probably suitable for inclusion.

Study selection

We identified relevant studies by examining the titles and abstracts of all studies or by obtaining a full text of the article if no abstract was available. The potentially eligible articles were reassessed by retrieving and evaluating the full text. Screening was conducted independently by two reviewers (P. H. and J. Z.). Inter-reviewer reliability for the study selection process was determined by the Kappa test. The consistency of our study was 61.3%. In case of disagreement for inclusion or exclusion, the issue was discussed until consensus was achieved by the reviewers (P. H. and J. Z.).

Data collection process

Data were collected by two independent review authors (P. H. and J. W.). Efforts were made to contact authors for additional data if the articles were suitable for a meta-analysis. Authors were asked to provide mean values and standard deviations for primary outcomes including FM, FFM and the percentage of FM. We attempted to send the second request if our first request did not yield a response. The study was excluded from the meta-analyses if the author was unable to provide additional data.

Data items

The following data were extracted from the included studies: study design, year of publication, location, demographic characteristics of the participants, definition of exposure, measuring technology of body composition, outcome and potential sources of bias.

Risk of bias in individual studies

All the authors assessed the risk of bias independently using the Newcastle–Ottawa Scale (NOS): (1) representativeness of the exposed cohort, (2) comparability of groups, (3) blinding of investigators who measured outcomes, (4) the time and completeness of follow-up, (5) contamination bias and (6) other potential sources of bias. Articles were scored as follows: ≥7 = high quality (NOS).

Summary measures

We calculated the mean difference and 95% CI of outcome at each postnatal age point between the formula-fed and breast-fed groups.
Synthesis of results

We performed a meta-analysis on studies that reported the outcomes (FM, FFM and the percentage of FM) between formula-fed and breast-fed groups at the following time points: 32-week corrected gestational age, 36-week gestational age, term, 3-month corrected age, 6-month corrected age and 12-month corrected age. We calculated the mean difference and 95% CI of outcome at each postnatal age point between the formula-fed and breast-fed groups. The $\chi^2$ test for Cochrane’s Q statistic and $I^2$ were used to test heterogeneity\(^{15}\). A fixed-effects meta-analysis was undertaken with RevMan 5 software (The Cochrane Collaboration) by using the inverse variance method ($P\geq0.05$; $\chi^2$ test). In contrast, a random-effects meta-analysis was carried out. This method was performed separately for each postnatal age point.

Risk of bias across studies

Publication bias was assessed using funnel plots.

Additional analyses

We intended to conduct subgroup analyses for sex and the same measuring technique of outcome.

Results

Study selection and characteristics

The characteristics of included and excluded studies are outlined in Fig. 1. A total of 630 articles were retrieved by search strategy, and eight articles were additionally identified by assessing the references of the retrieved articles and other sources. In total, 206 articles were removed as they were duplicate records of the same report through reference management software and manual screening. After examination of titles and abstracts, thirty articles were considered relevant; six studies were included and twenty-four studies were excluded after full-text review for the following reasons: the articles included breast-fed infants or formula-fed infants separately\(^{16,17}\); the primary outcomes were not reported\(^{18–23}\); the measurement method of body composition was skinfold thickness only\(^{24}\); articles were reviews\(^{25–27}\); the subjects were not preterm infants\(^{28,29}\); the language used was not English\(^{30–32}\); the studies were randomised-controlled trials\(^{33,34}\); and the studies were conference publications\(^{35–37}\).

Altogether, six studies were included in this systematic review\(^{38–43}\) (Table 1). We made efforts to contact the authors of three studies because data in their articles for meta-analysis were incomplete\(^{35–37}\), one author replied but was unable to provide additional data\(^{35}\), and we therefore excluded the three studies from the meta-analysis. All studies were longitudinal. The main technique used to measure body composition was dual-energy X-ray absorptiometry (DXA)\(^{38,40–43}\), and the other techniques used included body electrical impedance analysis\(^{39}\). Measurements of outcomes were conducted at a range of time points from birth to 12-month corrected age (Table 1). Only one study reported whether investigators were blinded when measuring the outcomes\(^{39}\). The feeding methods were prospectively defined in all studies, although the

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**Fig. 1.** Flow diagram of the search results.
Table 1. Characteristics of the six included studies in the systematic review

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Characteristics of population, study detail</th>
<th>Body-composition technique used, model used, adjusted for infancy (yes or no), reference used for adjustment, blinding assessment (yes or no)</th>
<th>Study groups: no. of infants</th>
<th>Age at body-composition measurement</th>
<th>Definitions of breast-feeding and formula-feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooke, 2010(36)</td>
<td>LS, 164 preterm infants with a GA ≤34 weeks and a birth weight ≤1750 g; the subjects have no systemic disease requiring no medication and are growing normally, UK</td>
<td>DXA, three-compartment model was used (FM, FFM and bone mass) with age-specific values(57), blinding not stated</td>
<td>BF: 25 FF: 139 Term 36-month CA 6-month CA 12-month CA</td>
<td>BF: 25 preterm infants were assessed prospectively and studied at the same time FF: 56 preterm infants fed with PTF between discharge and 6-month CA (energy 335 kJ/100 ml (80 kcal/100 ml), protein 2 g/100 ml, protein:energy ratio 2.75 g/100 ml); 57 preterm infants fed a TF between discharge and 6-month CA (energy 276.2 kJ/100 ml (66 kcal/100 ml), protein 1.4 g/100 ml, protein:energy ratio 2.1 g/100 ml); 26 preterm infants fed PTF between discharge and term and then the TF between term and 6-month CA</td>
<td></td>
</tr>
<tr>
<td>Amesz, 2010(42)</td>
<td>LS, 152 preterm infants with a GA ≤32 weeks or with a birth weight ≤1500 g; one of their main caretakers spoke Dutch or English, Amsterdam, Netherlands</td>
<td>DXA, two-compartment model, calculations performed by using age-specific values(58), blinding not stated</td>
<td>BF: 50 FF: 50 Term 6-month CA</td>
<td>BF: BM was fortified with standard BM fortifier until term CA. The predefined exclusively breast-feeding was that at least 80% of the total milk intake was BM. Infants receiving unfortified BM were supplemented with 200 IU (5 μg) of vitamin D daily. 50 infants were exclusively BF at term age, 19 of 50 at 3-month CA, 7 of 19 at 3-month CA FF: at term CA, 50 infants fed TF (energy 280 kJ/100 ml (67 kcal/100 ml), protein 1.47 g/100 ml, protein:energy ratio 2.19 g/100 ml) (Friso 1 normal; Friesland Foods)</td>
<td></td>
</tr>
<tr>
<td>Costa-Orvay, 2011(40)</td>
<td>LS, 38 preterm infants with GA ≤32 weeks and weight ≤1500 g; the subjects were recruited to the neonatology ward of Hospital Clinic in Barcelona, Spain. Barcelona, Spain</td>
<td>BIA, two-compartment model, FFM = total body water/water percentage of the FFM, FM = body weight – FFM, calculations of water percentage of the FFM was based on studies of Fomon et al.(59), blinded assessment Total body water(60) = 0.016 × 0.674 × weight – 0.038 × weight² + 3.84 foot length²/resistance</td>
<td>BF: 6 FF: 8 32-week CGA 36-week CGA</td>
<td>BF:BM 160 ml/kg per d + Enfamil Human Milk fortifier 4.5 g/kg per d FF: PTF, Alprem (Nestle) 160 ml/kg per d (in 100 g = 2117 kJ (506 kcal), protein 14.5 g, carbohydrate 53 g, fat 26 g) was given to the FF group</td>
<td></td>
</tr>
<tr>
<td>Wauben, 1998(41)</td>
<td>LS, 37 preterm infants. Additional data obtain from authors. Hamilton, Ontario, Canada</td>
<td>DXA, three-compartment model was used (FM, FFM and BMC) with age-specific values(61), blinding not stated</td>
<td>BF: 15 FF: 22 Term 36-month CA 6-month CA 12-month CA</td>
<td>BF: the predefined breast-feeding was over 60% of enteral intake as BM. 15 infants were fed BM at term age, ten at 3-month CA, 7 at 6-month CA. Supplemental Fe was provided at approximately 10 mg daily up to 6-month CA. 12 preterm infants received a new multinutrient fortifier and 12 preterm infants received Ca and P before hospital discharge FF: 22 infants exclusively TF. If infants received Fe-fortified formula, Fe was provided at approximately 10 mg daily up to 6-month CA. 12 infants received special premature infant formula (Preemie SMA, Wyeth-Ayerst) before hospital discharge All preterm infants received approximately 400 IU (10 μg) supplemental vitamin D after hospital discharge</td>
<td></td>
</tr>
<tr>
<td>Atkinson, 2000(42)</td>
<td>LS, 151 preterm infants were recruited in this study. Ontario, Canada</td>
<td>DXA, three-compartment model, calculations performed by using age-specific values(62), blinding not stated</td>
<td>BF: 27 FF: 34 Term</td>
<td>BF: the predefined BM was &gt;80% of total milk intake up to 3-month CA. Infants fed expressed mother’s milk with either added multidimensional fortifier or Ca and P during hospitalisation FF: exclusively or predominantly TF. Most infants received a special prematurity infant formula (Preemie SMA, Wyeth-Ayerst) while in the hospital</td>
<td></td>
</tr>
<tr>
<td>Pieltain, 2001(41)</td>
<td>LS, 54 healthy preterm infants, birth weight &lt;1750 g; Belgium</td>
<td>DXA, four-compartment model was used (FM, FFM, BMC, bone mineral content) with age-specific values(63), blinding not stated</td>
<td>BF: 20 FF: 34 32-week CGA 36-week CGA</td>
<td>BF: BM was supplemented with banked human milk as available and up to 3–4 % with two similar fortifiers: Eoprofin (Milupa) or BMF (Nutricia) FF: the group of FF received PTF Nenatal (Nutricia), Prematil (Milupa) or Premie (Wyeth)</td>
<td></td>
</tr>
</tbody>
</table>

LS, longitudinal study; GA, gestational age; DXA, dual-energy X-ray absorptiometry; FM, fat mass; FFM, fat-free mass; CA, corrected age; BF, breast-fed; FF, formula-fed; BM, breast milk; PTF, preterm formula; TF, standard term formula; BIA, body electrical impedance analysis; CGA, corrected gestational age; BMC, bone mineral content; BMD, bone mineral density.

* Quality of the cohort studies were assessed using Newcastle–Ottawa Scale, ≥7 = high quality.
definitions of feeding group varied (Table 1). FM, FFM and the percentage of FM of the feeding group for each study are shown in Table 2. Variables not normally distributed were not extracted(43).

Risk of bias within studies

The risk of bias of each study is presented in Table 1.

Synthesis of results

Both FFM and percentage of FM in the formula-fed group were significantly higher compared with the breast-fed group at 36-week corrected gestational age. The mean difference of the percentage of FM was 0·20 (95 % CI −1·11, 1·51) kg at 32-week corrected gestational age. No significant mean differences in FM were found between the formula-fed group and the breast-fed group at 32- and 36-week corrected gestational age (Fig. 2–4); two articles39,41 reported the outcomes at 32- and 36-week corrected gestational age. Percentage of FM was not provided in one study39 even after we contacted the author; therefore, we excluded this study from the analysis for the percentage of FM. Formula-fed infants had significantly higher FM than breast-fed infants at term. No significant differences were detected in FFM or the percentage of FM (Fig. 2–4). The variables were not normally distributed, and thus the outcomes are not presented as mean values and standard deviations(43). No significant differences were found in FM, FFM or the percentage of FM between the formula-fed and the breast-fed groups at 3-month, 6-month and 12-month corrected age (Fig. 2–4). The mean differences in FM were −0·05 (95 % CI −0·28, 0·17) kg at 3-month, −0·03 (95 % CI −0·32, 0·25) kg at 6-month, −0·09 (95 % CI −0·37, 0·19) kg at 12-month corrected age. The mean differences in FFM were 0·24 (95 % CI −0·19, 0·66) kg at 3-month and 0·08 (95 % CI −0·26, 0·42) kg at 12-month corrected age.

Pooled differences

Fig. 2–4 indicate pooled differences in FM, FFM and the percentage of FM between the formula-fed and breast-fed infants by postnatal 1 year of corrected age.

Risk of bias across studies

The funnel plots of studies at 32- and 36-week gestational age indicated no considerable publication bias.

Discussion

Summary of evidence

On the basis of the current available evidence from six studies with data available from 642 infants, we found significant complex differences in body composition between breast-feeding and formula-feeding on preterm infants at 1 year of corrected age. The outcomes of the meta-analysis indicated that formula-fed infants had higher FM at 32-week corrected gestational age, 36-week corrected gestational age and term. By 3-month corrected age, this difference was no longer

Table 2. Body composition data of included studies in the systematic review

<table>
<thead>
<tr>
<th>First author, year (reference), study groups: no. of infants</th>
<th>Age</th>
<th>Fat mass</th>
<th>Fat-free mass</th>
<th>Percentage of fat mass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BF</td>
<td>FF</td>
<td>BF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Cooke, 201038</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BF: 25</td>
<td></td>
<td>Term</td>
<td>0·331</td>
<td>0·128</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8-month CA</td>
<td>1·365</td>
<td>0·527</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-month CA</td>
<td>1·934</td>
<td>0·658</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-month CA</td>
<td>2·153</td>
<td>0·645</td>
</tr>
<tr>
<td>Amesz, 201043</td>
<td></td>
<td>Term</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BF: 50</td>
<td></td>
<td>6-month CA</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cosat-Orvay, 201139</td>
<td></td>
<td>32-week CGA</td>
<td>0·111</td>
<td>0·062</td>
</tr>
<tr>
<td>FF: 8</td>
<td></td>
<td>36-week CGA</td>
<td>0·202</td>
<td>0·049</td>
</tr>
<tr>
<td>Wauben, 199840</td>
<td></td>
<td>Term</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BF: 15</td>
<td></td>
<td>3-month CA</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-month CA</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-month CA</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pieltain, 200141</td>
<td></td>
<td>32-week CGA</td>
<td>0·071</td>
<td>0·035</td>
</tr>
<tr>
<td>FF: 34</td>
<td></td>
<td>36-week CGA</td>
<td>0·20</td>
<td>0·054</td>
</tr>
<tr>
<td>Atkinson, 200042</td>
<td></td>
<td>Term</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

BF, breast-fed; FF, formula-fed; CA, corrected age; CGA, corrected gestational age.
Our observed differences in body composition between formula-fed infants and breast-fed infants are inconsistent with the results of the meta-analysis comparing the effects of breast milk on body composition with formula-feeding in healthy, term infants\(^{(47)}\). The reasons may be that preterm infants have fewer nutrient reserves at birth than full-term infants, and are often fed preterm formula or supplementation of mother’s milk with human milk fortifiers. Moreover, owing to immature metabolic pathways for nutrient utilisation and/or an immature growth hormone/insulin-like growth factor axis, the absorption and assimilation of nutrients are limited. Meanwhile, although late preterm infants (gestational age between 34 and 36 weeks) are usually able to breast-feed, they are more likely to experience difficulty in establishing successful breast-feeding than term infants because preterm infants’ oro-buccal coordination and swallowing mechanisms may not be fully matured\(^{(48)}\). Furthermore, a systematic review was conducted by Arenz et al\(^{(49)}\), which analysed the association of breast-feeding with childhood obesity. Although the results showed that breast-feeding reduced the risk of obesity in apparent, with a reverse trend and lower FM in formula-fed infants. Formula-fed infants had lower FM than their breast-fed counterparts at 32-week corrected gestational age but higher FM from 36-week corrected gestational age to 12-month corrected age. These findings are biologically plausible. Preterm infants were fed preterm formula before term. Preterm formula contains higher levels of protein and energy than term formula. At the initial stages of enteral feeding with high energy intakes\(^{(41)}\), rapid weight gain reflects an increase in FM\(^{(45)}\), which is followed by an increase in muscle mass later. Meanwhile, because the ratio of protein-energy in the diet will influence body composition\(^{(46)}\), the lower protein-energy ratio of breast milk may lead to less FFM deposition with excess energy deposited as fat. For this reason, the lower protein intake in breast-fed infants may explain the observed higher FM compared with formula-fed infants after term.

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**Fig. 2.** Pooled mean differences in fat mass between the formula-fed group and the breast-fed group. CGA, corrected gestational age.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Formula-feeding group</th>
<th>Breast-feeding group</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>32-week CGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooke 2010</td>
<td>0.67</td>
<td>0.10</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Subtotal (95 % CI)</td>
<td>0.67</td>
<td>0.10</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Subtotal (95 % CI)</td>
<td>0.67</td>
<td>0.10</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.77 (P = 0.00)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36-week CGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooke 2010</td>
<td>0.67</td>
<td>0.10</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Subtotal (95 % CI)</td>
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<td>0.10</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Subtotal (95 % CI)</td>
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<td>0.10</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.77 (P = 0.00)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

---

**Fig. 3.** Pooled mean differences in fat-free mass between the formula-fed group and the breast-fed group. CGA, corrected gestational age; CA, corrected age.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Formula-feeding group</th>
<th>Breast-feeding group</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>32-week CGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooke 2010</td>
<td>0.67</td>
<td>0.10</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Subtotal (95 % CI)</td>
<td>0.67</td>
<td>0.10</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Subtotal (95 % CI)</td>
<td>0.67</td>
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<td>10</td>
<td>0.02</td>
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<td>Test for overall effect: Z = 2.77 (P = 0.00)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>36-week CGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooke 2010</td>
<td>0.67</td>
<td>0.10</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Subtotal (95 % CI)</td>
<td>0.67</td>
<td>0.10</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Subtotal (95 % CI)</td>
<td>0.67</td>
<td>0.10</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.77 (P = 0.00)</td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

---

**Study or subgroup**

Cooke 2010

**Formula-feeding group**

Mean: 0.67
SD: 0.10
Total: 10

**Breast-feeding group**

Mean: 0.02
SD: 0.05
Total: 10

Mean difference: 0.67 – 0.02 = 0.65
IV, Random 95 % CI: 0.53 – 0.79

**Test for overall effect:** Z = 2.77 (P = 0.00)
Koo & Hockman(17) found that absolute FFM and FM were ratio had a higher absolute FFM and lower percentage of FM(51). reported that formula-fed infants having higher protein:energy
studies, publication bias, confounding factors and potential
the validity of the meta-analyses, including the types of
this effect was no longer apparent, with a trend towards reversal
mean BMI. The outcome of our meta-analysis indicated that
small. Promotion of breast-feeding was not likely to reduce
BMI was lower among breast-fed infants, but the difference was
breast-feeding and BMI throughout life suggested that mean
This result supports our analysis of outcomes obtained
Using different in vivo measurement techniques of body

Limitations

Our study has several limitations. First, the percentage of FM
depends on FFM; therefore, it has been recommended to adjust FM and FFM for height to create independent measures(53) (fat-free mass index (FFMI) and fat mass index (FMI)). However, we could not collect data on FFMI or FMI because of lack of data in included articles. Second, as suggested by Cooke et al.(52), sex was an additional significant independent variable, resulting in an increase in FM and bone mineral content in female infants(54). Nevertheless, we were unable to examine the effect of sex because only a limited number of studies reported outcomes by sex.

Third, breast-feeding was assessed prospectively in all included studies, which limited the recall bias. However, the definition of feeding groups varied widely, and none of the studies used WHO criteria for exclusive breast-feeding, which indicates that a contamination bias may represent an important source of heterogeneity. Moreover, one article did not report the exact definition. Fourth, the infant formulae contained higher levels of long-chain PUFA (LCPUFA), Ca and P. Although the study of de Jong et al.(55) suggested that LCPUFA supplementation does not alter neurological function, no data were available on its effect on body composition. Fifth, one study exploring the association between psychosocial risk factors and

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Formula-feeding group Mean</th>
<th>SD</th>
<th>Total</th>
<th>Breast-feeding group Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight (%)</th>
<th>Mean difference IV, Random 95% CI</th>
<th>Mean difference IV, Random 95% CI</th>
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<td>36-week CGA</td>
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<td>34</td>
<td>9.5</td>
<td>2.6</td>
<td>20</td>
<td>100.0</td>
<td>3.70 [-1.81, 5.59]</td>
<td>3.70 [-1.81, 5.59]</td>
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<tr>
<td>Pietrain 2001</td>
<td>19</td>
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<td>34</td>
<td>22</td>
<td>6</td>
<td>27</td>
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<tr>
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<td></td>
<td>67</td>
<td></td>
<td>100.0</td>
<td>0.92</td>
<td>1.17 [-5.42, 4.88]</td>
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</tr>
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<td>Heterogeneity.</td>
<td>$I^2 = 19.15; \bar{I}^2 = 28.01$, $df = 2 (P &lt; 0.0001)$; $I^2 = 93%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.24</td>
<td>0.41</td>
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<tr>
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<td></td>
<td></td>
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<td>1.64</td>
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<tr>
<td>3-month CA</td>
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<td>5.1</td>
<td>83</td>
<td>25.8</td>
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<td>25</td>
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<td>-0.70 [-4.10, 2.70]</td>
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<tr>
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<td>8.8</td>
<td>32</td>
<td>30.1</td>
<td>6.4</td>
<td>15</td>
<td>39.3</td>
<td>-4.60 [-9.50, 0.30]</td>
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<tr>
<td>Wauben 1998</td>
<td>19.6</td>
<td>5.4</td>
<td>22</td>
<td>23.3</td>
<td>5.5</td>
<td>25</td>
<td>32.8</td>
<td>-2.40 [-5.12, 0.32]</td>
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<tr>
<td>Subtotal (95 % CI)</td>
<td>138</td>
<td></td>
<td></td>
<td>67</td>
<td></td>
<td>100.0</td>
<td>0.92</td>
<td>1.17 [-5.42, 4.88]</td>
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<td>1.64</td>
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<td>6-month CA</td>
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<td>32.1</td>
<td>9.1</td>
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<td>91.0</td>
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<tr>
<td>Cooke 2010</td>
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<td>27.9</td>
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<td>15</td>
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<tr>
<td>Wauben 1998</td>
<td>28.4</td>
<td>8.1</td>
<td>22</td>
<td>27.9</td>
<td>4.8</td>
<td>15</td>
<td>30.1</td>
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<td>1.66</td>
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<tr>
<td>12-month CA</td>
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<td>83</td>
<td>25.4</td>
<td>4.8</td>
<td>25</td>
<td>70.7</td>
<td>-1.00 [-3.17, 1.17]</td>
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<td>5.6</td>
<td>83</td>
<td>23.9</td>
<td>4.8</td>
<td>15</td>
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<td>0.00 [-3.37, 3.37]</td>
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<td>Wauben 1998</td>
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<td>5.6</td>
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<td>23.9</td>
<td>4.8</td>
<td>15</td>
<td>29.3</td>
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<td></td>
<td>40</td>
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<td>0.92</td>
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<tr>
<td>Test for overall effect: $Z^2 = 0.76 (P = 0.45)$</td>
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<td>0.66</td>
<td>1.66</td>
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</table>

Test for subgroup differences: $I^2 = 15.50$, $df = 4 (P = 0.004)$, $\bar{I}^2 = 74.2\%$

Fig. 4. Pooled mean differences in the percentage of fat mass between the formula-fed group and the breast-fed group. CGA, corrected gestational age; CA, corrected age.

childhood significantly, results from another systematic review carried out by Owen et al.(50) investigating the relation between breast-feeding and BMI throughout life suggested that mean BMI was lower among breast-fed infants, but the difference was small. Promotion of breast-feeding was not likely to reduce mean BMI. The outcome of our meta-analysis indicated that breast-fed infants had lower FM at 32-week corrected gestational age, 36-week corrected gestational age and term compared with formula-fed infants. By 3-month corrected age, this effect was no longer apparent, with a trend towards reversal and higher FM in breast-fed infants. Several drawbacks limited the validity of the meta-analyses, including the types of studies, publication bias, confounding factors and potential heterogeneity between studies.

Some evidences support our outcomes. Investigators have reported that formula-fed infants having higher protein:energy ratio had a higher absolute FFM and lower percentage of FM(51). Koo & Hockman(17) found that absolute FFMI and FM were increased in infants fed standard formula. Furthermore, in the study of Cooke et al.(52), absolute FM and FM were higher in the group of infants fed energy- and protein-enriched formulæ, but the percentage of FM did not differ.

DXA is used to evaluate the composition of growth in a single scan. It is non-invasive and of low health risk to the infant, and has therefore been widely used in our included studies. We performed subgroup analyses of studies in which values were measured using this technique. This result supports our analysis of outcomes obtained using different in vivo measurement techniques of body composition.

Limitations

Our study has several limitations. First, the percentage of FM depends on FFM; therefore, it has been recommended to adjust FM and FFM for height to create independent measures(53) (fat-free mass index (FFMI) and fat mass index (FMI)). However, we could not collect data on FFMI or FMI because of lack of data in included articles. Second, as suggested by Cooke et al.(52), sex was an additional significant independent variable, resulting in an increase in FM and bone mineral content in female infants(54). Nevertheless, we were unable to examine the effect of sex because only a limited number of studies reported outcomes by sex.

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breast-feeding discontinuation suggested that maternal depression can lead to early discontinuation of breast-feeding\(^{56}\). Meanwhile, women who choose formula-feeding often lack confidence in their ability to breast-feed, because they think formula may be better for their infants or their milk is inadequately supplied. Therefore, the body compositions were probably affected by psychosocial factors. Finally, none of the included articles mentioned the blinding of data collectors\(^{38-43}\).

**Conclusion**

In summary, this systematic review suggests that formula-feeding is associated with altered body composition from delivery to term in preterm infants compared with breast-feeding. The effects of formula-feeding on preterm infant body composition from term to 1 year of corrected age are inconclusive. Our findings enable to confirm the possible contributions of breast-feeding and formula-feeding on risk of obesity in childhood and adult life.

The number of studies included in our analysis is limited, and the findings from our meta-analysis should be confirmed by future studies. Meanwhile, well-designed studies are required to define the effect of formula-feeding on body composition compared with breast-feeding.

**Acknowledgements**

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B. L. assisted P. H. and J. Z. in formulating the research questions and supervising the quality of this manuscript. Designing the study and screening of the articles were conducted by two reviewers (P. H. and J. Z.). P. H. and J. W. collected data. J. Z. and Y. Y. analysed the data. P. H. and J. W. wrote the article, and J. W. revised the article.

None of the authors has any conflicts of interest to declare.

**Supplementary material**

For supplementary material/s referred to in this article, please visit http://dx.doi.org/doi:10.1017/S0007114516001720

**References**


