# Effect of breastfeeding compared with formula feeding on infant body composition: a systematic review and meta-analysis[1–3]

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**ABSTRACT**

**Background:** Early-life nutrition may influence later body composition. The effect of breastfeeding and formula feeding on infant body composition is uncertain.

**Objective:** We conducted a systematic review and meta-analysis of studies that examined body composition in healthy, term infants in relation to breastfeeding or formula feeding.

**Design:** PubMed was searched for human studies that reported the outcomes fat-free mass, fat mass, or the percentage of fat mass in breastfed and formula-fed infants. Bibliographies were hand searched, and authors were contacted for additional data. The quality of studies was assessed. Differences in outcomes between feeding groups were compared at prespecified ages by using fixed-effects analyses except when heterogeneity indicated the use of random-effects analyses.

**Results:** We identified 15 studies for inclusion in the systematic review and 11 studies for inclusion in the meta-analysis. In formula-fed infants, fat-free mass was higher at 3–4 mo [mean difference (95% CI): 0.13 kg (0.03, 0.23 kg)], 8–9 mo [0.29 kg (0.09, 0.49 kg)], and 12 mo [0.30 kg (0.13, 0.48 kg)], and fat mass was lower at 3–4 mo [−0.09 kg (−0.18, −0.01 kg)] and 6 mo [−0.18 kg (−0.34, −0.01 kg)] than in breastfed infants. Conversely, at 12 mo, fat mass was higher in formula-fed infants [0.29 kg (−0.03, 0.61 kg)] than in breastfed infants.

**Conclusion:** Compared with breastfeeding, formula feeding is associated with altered body composition in infancy. *Am J Clin Nutr* 2012;95:656–69.

## INTRODUCTION

The relation between breastfeeding and body composition is of considerable relevance to human health. Particular interest surrounds the potential role of infant feeding in influencing body composition, overweight, and obesity in later life. Systematic reviews that examined associations between early feeding and later-life obesity or BMI have been inconclusive (1, 2). This is perhaps unsurprising given the considerable between-study heterogeneity and the importance of confounding in long-term observational studies. Any effect of breastfeeding on adult weight and body composition might be mediated through, or share common biological pathways with, effects on infant body composition, and the accumulation of fat mass relative to body weight is maximal in infancy (3). Therefore, we considered it relevant to question whether an effect of infant feeding on body composition can be identified in the preweaning and early postweaning period when any relation might be expected to be more pronounced, and the influence of potential confounding factors are more limited.

Growth patterns differ between breastfed and formula-fed infants, and by 12 mo of age, formula-fed infants weigh, on average, 400–600 g more than breastfed infants (4, 5). Attempts to measure the effect of infant feeding on body composition have been limited by the variety of techniques used and small sample sizes, and individual studies have reported conflicting results with respect to both the direction and magnitude of effect (6–8). Body composition changes rapidly and nonlinearly over the first year of life (9), and therefore, comparisons between individual studies have also been complicated by the range of postnatal ages at which measurements have been made.

In this study, we present a systematic review and meta-analysis of longitudinal and cross-sectional studies that were performed in infancy and examined body composition in vivo in relation to breastfeeding and formula feeding.

## SUBJECTS AND METHODS

### Literature search

A systematic review of published studies that reported outcomes of healthy, term (37–42 wk of gestation) infants (0–12 mo of age) was undertaken in accordance with guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (10). A protocol was developed (by CG) and reviewed by all authors. The outcomes studied were fat mass (kg), fat-free mass (kg), and the percentage of fat mass. We included studies that used a model of ≥2 compartments with determination of at least one compartment by using one of the following in-vivo techniques: TBK[4], TOBEC, isotope dilution, ADP, DXA, MRI, or computerized tomography. Studies in which body composition was derived through the measurement of skinfold thickness

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[4] Abbreviations used: ADP, air-displacement plethysmography; DXA, dual-energy X-ray absorptiometry; TBK, total-body potassium determination; TOBEC, total-body electrical conductivity.

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were excluded because of the poor ability of this technique to predict body composition in infancy (11, 12). Types of exposure were breastfeeding (exclusive or predominant) and formula feeding (exclusive or predominant) as defined in each study. No limit was applied with respect to the duration of the feeding method in either group. For inclusion, formula should have been a standard, commercial cow milk–based product, comparison of breastfed and formula-fed groups must have occurred at the same time points, and at least one measure of body composition must have been performed in the first postnatal year.

A search was conducted in PubMed (http://www.ncbi.nlm.nih.gov) for studies published before 24 March 2011 in any language by using the following MEDLINE Medical Subject Headings terms, with limitation to human studies: [(breast feeding) OR (infant formula) OR (infant nutritional physiologic phenomena)] AND [(body composition) OR (bioelectrical impedance) OR (total body electrical conductivity) OR (air-displacement plethysmography) OR (absorptiometry, photon) OR (total body potassium) OR (magnetic resonance imaging) OR (tomography, X-ray computed) OR (isotope dilution)].

### Data extraction

A literature search was conducted (by CG and assisted by JRCP), and relevant studies were identified by evaluating the abstract or obtaining a full copy of the article if no abstract was available. Reference lists of articles retrieved were hand searched for studies appropriate for inclusion. Whenever possible, forward citations of studies retrieved during the literature search were traced. Review articles and commentaries were excluded after hand searching reference lists.

Data on the study design, location, population, exposure classification, technique of body-composition measurement, outcome, and potential sources of bias were extracted (independently by CG and KML and checked by MJH and SS). Study quality was assessed in relation to the following study biases: blinding to the feeding group by investigators who measured outcomes, definition of feeding groups (in particular, the extent of contamination bias that arose from formula feeding in the breastfed group), and method of assessment of feeding status (prospective or retrospective). In studies in which body-composition data were not presented in a form suitable for a meta-analysis, efforts were made (by CG) to contact the author to obtain these data. Authors were asked to provide means and SDs for fat/adipose tissue mass, fat-free mass, and the percentage of fat mass by feeding group. If no response to 2 requests was received, or if the author was unable to provide additional data, the study was excluded from meta-analyses. When only sex-specific values were presented, these values were pooled by using a standard formula for the combination of mean and SD data (13).

### Analysis

A meta-analysis was carried out of studies that reported differences in outcomes (fat mass, fat-free mass, and the percentage of fat mass) between formula-fed and breastfed groups at the following time points: 1–2, 3–4 (representing the preweaning period), 6 (weaning), 8–9, and 12 (representing the postweaning period) mo. The mean difference (95% CI) between outcomes in the formula-fed and breastfed groups was calculated at each postnatal age point. When a study examined the same population at 2 postnatal ages and both ages fell within one predefined point, which, therefore, rendered both ages eligible for inclusion (eg, when data were collected at 3 and 4 mo), data from the later age was included in the meta-analysis. When data were obtained from one population at the same postnatal age by using 2 alternate methods, the method with the smallest SD was included in the subsequent meta-analysis. To examine the robustness of these assumptions, analyses were repeated by using the alternate values to determine whether this led to a different conclusion.

A fixed-effects meta-analysis was undertaken with RevMan 5 software (The Cochrane Collaboration) by using the inverse-variance method. This method was performed separately for each postnatal age point. Heterogeneity was assessed by using the chi-square test for Cochrane's Q statistic (14) and by calculating $I^2$ (15). When heterogeneity was present ($P < 0.05$; chi-square test), a random-effects meta-analysis was carried out. In this case, the pooled difference was the estimate of the average effect across study populations because studies were assumed to have different underlying effects. In contrast, for fixed-effects analyses, studies were assumed to have the same underlying effect, which was estimated by using the pooled difference. Results were illustrated by using forest plots. Funnel plots were used to investigate asymmetry.

Subgroup analyses were planned of studies that were performed by using the same body-composition technique, when ≥3 studies reported results at comparable postnatal ages, and of sex-specific values. A subgroup analysis of results by sex may be subject to selection bias because studies may only report results by sex if a difference is observed. Therefore, a subgroup analysis by sex was only carried out if the meta-regression showed sex differences to be significant, and if data were available for the majority of studies at the relevant time point.

## RESULTS

The literature search is outlined in **Figure 1**. The search strategy identified 702 publications; an additional 8 articles were located after bibliographic review of retrieved articles (16–23). One article was unavailable (in full or abstract form) for review (24). After screening of abstracts, the full texts of 35 articles were reviewed to assess eligibility. Twenty studies were excluded after full-text review for the following reasons: only breastfed infants were included, with no comparative formula-fed group (25); body composition was determined by using skinfold thickness only (21, 26–30); articles were review articles (4, 31–34); the feeding method was not provided (19, 22, 35, 36); percentages of fat mass or adiposity data were not provided (37–39); and study cohorts (40) were part of a larger, included cohort (41).

### Identified studies

Fifteen studies remained for inclusion in the systematic review (6–8, 16–18, 20, 23, 41–47) (**Table 1**). For the meta-analysis, attempts were made to contact authors of 7 studies for additional data (6, 16, 41–43, 45, 47); 5 authors replied (6, 16, 41, 42, 47), but one author was unable to provide data (47). There was considerable heterogeneity with respect to study design. The majority of studies used a longitudinal design, although 3 studies

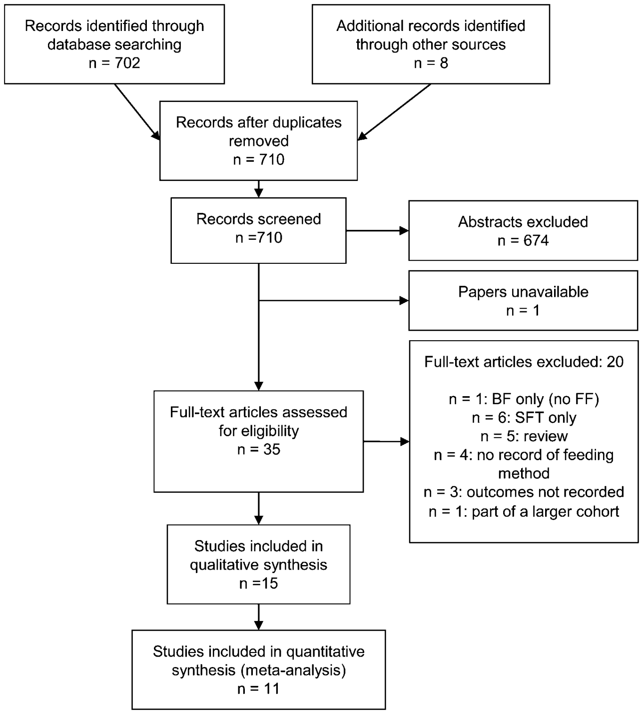


**FIGURE 1.** Flowchart of the search strategy used in this review set out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The relevant number of papers at each point is provided. BF, breastfed; FF, formula fed; SFT, skinfold thickness.

were cross sectional (17, 41, 46). A wide range of techniques were used to measure body composition [ie, TBK (47), isotope dilution (8, 23, 41, 44, 46), TOBEC (7, 17, 46), DXA (43, 45), MRI (20), ADP (16, 18, 42), and a multicomponent technique that incorporated isotope dilution, TBK, and DXA (6)]. No studies were shown to assess body composition in infancy by using computerized tomography. Measurements were performed at a range of time points during the first year (Table 1).

With respect to study quality, no study reported whether measurements were performed by investigators blinded to the feeding group. The feeding method was prospectively defined in all studies except one study (17), although the definitions used for feeding groups varied in studies (Table 1). Information provided on weaning (Table 1) indicated that feeding at time points ≥6 mo was no longer predominantly breast-milk feeding even in those groups designated as breastfed groups. Therefore, for time points ≥6 mo, the breastfed group represented originally breastfed infants. In 8 of the 15 studies included, age-specific values were used for hydration and density of fat-free mass (3). Individual study values for fat mass, fat-free mass, and the percentage of fat mass that were represented by feeding group are shown in **Table 2**.

## Body composition at 1–2 mo

There were no significant mean differences in fat mass, fat-free mass, or the percentage of fat mass between the formula-fed and breastfed groups (**Tables 3–5**; *see* Figure 1 under "Supplemental data" in the online issue) at 1–2-mo postnatal age. One study (45), in which no significant difference was shown in the percentage of fat mass at 2 mo, did not report SDs (and these data were unavailable from the authors) and was, therefore, excluded from the meta-analysis. For meta-analyses, data of fat mass and the percentage of fat mass from Butte et al (46) that was obtained by using isotope dilution had a narrower SD than did values obtained by using TOBEC for the same cohort; therefore, isotope-dilution data were included; for fat-free mass, data derived by using TOBEC were included. When Anderson (16) and de Bruin et al (7) reported values at 1 and 2 mo, the 2-mo values were included. The repetition of analyses by using alternate values for the studies by Butte et al (46), Anderson (16), and de Bruin et al (7) did not alter the significance or direction of results.

## Body composition at 3–4 mo

Formula-fed infants had significantly lower fat mass, significantly higher fat-free mass, and a significantly lower percentage of fat mass than did breastfed infants at 3–4 mo age (Tables 3–5; *see* Figure 2 under "Supplemental data" in the online issue). Despite contact with the author, SDs were unavailable from one study (47) (which also reported a significantly higher fat-free mass and lower percentage of fat mass in formula-fed girls, but not boys, at 3 mo) and was excluded from meta-analyses. Data determined by using TOBEC by Butte et al (46) had narrower SDs than did data determined by using dilutional techniques; therefore, TOBEC data were included in our meta-analysis. The repetition of analyses by using alternate values for the study by Butte et al (46) did not alter the significance, direction, or magnitude of results.

## Body composition at 6 mo

Formula-fed infants had significantly lower fat mass and percentage of fat mass than did breastfed infants at 6 mo. No significant differences were detected in fat-free mass (Tables 3–5; *see* Figure 3 under "Supplemental data" in the online issue). Despite attempts to contact authors, additional data were unavailable for 1 study (43), which was excluded from meta-analyses. The study (43) reported a significant positive association between breastfeeding at 6 mo and the percentage of fat mass at 6 mo measured by using DXA. This association was present for the truncal percentage of fat mass but not for the peripheral percentage of fat mass.

## Body composition at 8–9 mo

Formula-fed infants had significantly higher fat-free mass than did breastfed infants at 8–9 mo. No significant differences were detected in fat mass or the percentage of fat mass (Tables 3–5; *see* Figure 4 under "Supplemental data" in the online issue).

## Body composition at 12 mo

Formula-fed infants had significantly higher fat-free mass than did breastfed infants at 12 mo. No significant differences were detected in fat mass or the percentage of fat mass (Tables 3–5; *see* Figure 5 under "Supplemental data" in the online issue).

## Funnel plots

Funnel plots of studies at 3–4 mo (*see* Figure 7 under "Supplemental data" in the online issue) showed no visual evidence of

**TABLE 1**
Details of studies included in systematic review[1]

| First author, year (reference) | Population and study detail and how recruited | Body-composition technique used, compartment measured, model used, adjusted for infancy (yes or no), reference used for adjustment, and blinded assessment (yes or no) | Study groups: no. of infants | Age at body-composition measurement | Breastfeeding definition, prospective or retrospective data, type of formula |
|---|---|---|---|---|---|
| Shepherd, 1988 (47) | LS; 38–42 wk, healthy; excluded: diabetes, medications, small for dates (not defined). 107 subjects were recruited, and 25 subjects dropped out. Growth between 10th and 90th percentile for both groups.<br>Authors were unable to provide additional data. | TBK. 4-compartment model: body mass = FM + FFM (FFES + BCM +ECW).<br>FFES + BCM calculated from references 19 and 48 by using age-specific values. Blinding not stated.<br>ECW derived from a normogram (49). | BF: 34<br>FF: 48 | 10 d<br>3 mo | Feeding groups predefined.<br>FF: exclusively fed whey-predominant formula (NAN, Nestlé), except for water supplementation, for entirety of study.<br>BF: exclusive, except for water supplementation, for entirety of study. |
| Butte, 1995 (46) | CSS; 20 term, healthy infants examined at 1 mo of age, and 20 term, healthy infants examined at 4 mo. Texas. | Infants examined by using 2 techniques at the same time point.<br>Doubly labeled water dilution: 2-compartment model.<br>TOBEC: 2-compartment model.<br>Calculations by using FFM constants from Fomon et al (3) and age-specific values. Blinding not stated.<br>Calculation of FFM from reference 50, adjusted for infancy (yes). Blinding not stated. | BF: 10<br>FF: 10<br>BF: 10<br>FF: 10 | 1 mo<br><br>4 mo | Feeding determined prospectively.<br>FF: exclusive Enfamil (Mead Johnson and Company) or Similac (Ross Laboratories) formula. At 4 mo of age, 6 FF infants received supplemental foods, which provided 8 ± 11% of energy.<br>BF: exclusive. No BF infants received supplemental foods during the study. |
| Bellu, 1997 (17) | CSS; 79 healthy, AGA, term infants measured at 12 mo of age. Single hospital (Milan, Italy). Restricted to first or second child; maternal age: 20–30 y; maternal pregravid weight: 80–100% of ideal weight; maternal education: high school diploma or greater. | TOBEC: 2-compartment model. Calculation of FFM from reference 50 by using age-specific values. Blinding not stated. | BF: 26<br>FF: 55 | 12 mo | Feeding determined by retrospective interview.<br>BF: exclusively BF until 6 mo of age (weaning allowed >5 mo of age), FF: BF for <2 mo.<br>Age of introduction of solids not significantly different between BF and FF groups. Cow milk introduced later in the BF group (9.5 mo) than in the FF group (7.7 mo). |
| Motil, 1997 (8) | LS; 20 healthy, term infants. Texas. | $H_2{}^{18}O$ dilution. 2-compartment model. Calculations by using FFM constants from Fomon et al (3) and age-specific values. Blinding not stated. | BF: 10<br>FF: 10 | 6 wk<br><br>3 mo<br><br>18 wk<br>6 mo | Feeding groups predefined. BF assessed prospectively.<br>BF: exclusive until 6 mo of age, except in 2 infants who received formula >18 wk of age.<br>FF: exclusively FF (variety of formula feeds used). |

*(Continued)*

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**TABLE 1** (*Continued*)

| First author, year (reference) | Population and study detail and how recruited | Body-composition technique used, compartment measured, model used, adjusted for infancy (yes or no), reference used for adjustment, and blinded assessment (yes or no) | Study groups: no. of infants | Age at body-composition measurement | Breastfeeding definition, prospective or retrospective data, type of formula |
|---|---|---|---|---|---|
| de Bruin, 1998 (7) | LS; healthy, birth weight >2500 g, vaginally delivered infants of white, nonsmoking mothers; recruited through community midwives, Rotterdam, Netherlands. 92 infants recruited, 46 excluded. | TOBEC: 2-compartment model. Calculation of FFM from reference 36 by using age-specific values. Blinding not stated. | BF: 23<br>FF: 23 | 1 mo<br>2 mo<br>4 mo<br>8 mo<br>12 mo | Feeding groups predefined. Breastfeeding assessed prospectively.<br>BF: exclusively BF at 1 and 2 mo of age. 7 of 24 BF and 6 of 23 FF infants supplemented at 4 mo of age (eg, fruit and vegetables); only one infant supplemented >10% of intake (24%). At 8 mo of age, 5 BF infants still received some BM. At 12 mo of age, no infant received BM. All formula came from a single batch (Nutrilon Premium; Nutricia Inc, Zoetermeer, Netherlands). |
| Jiang, 1998 (23) | CSS; healthy, full-term infants. Xinhui, Guangdong Province, China. | Deuterium dilution. 2-compartment model. | BF: 11<br>FF 11 | 4 mo | BF: at 4 mo of age, no weaning foods or energy-containing foods provided; at 6 mo of age, some weaning but BF still defined as high. |
| | | Calculations by using FFM from Fomon et al (3) and age-specific values. Blinding not stated. | BF: 9<br>FF: 10 | 6 mo | FF: at 6 mo of age, some weaning such that <30% of energy provided by FF. |
| Butte, 2000 (6) | LS; 76 healthy, term infants; nonsmoking mothers. Single city, Texas.<br>Additional data obtained from authors. | Multicomponent model:<br>TBM = FFM (TBW + protein + glycogen + BMC + nonosseous material) + FM<br>TOBEC-FFM; Deuterium dilution-TBW; TBK-protein; DXA-BMC<br>Calculations by using FFM constants from Fomon et al (3) and age-specific values. Blinding not stated. | BF: 40<br>FF: 36 | 0.5 mo<br>3 mo<br>6 mo<br>9 mo<br>12 mo | Feeding groups predefined.<br>BF: Exclusively BF for 4 mo in all but 4 cases (weaned at approximately 100 d of age). 100%, 80%, 58%, 38% of the BF group still were breastfeeding at 3, 6, 9, and 12 mo of age, respectively. 0%, 40%, 48%, 30% of the BF group were given formula by 3, 6, 9, and 12 mo of age, respectively. FF: exclusively FF; 9 of 36 infants were given small amounts of cereal or fruit before 4 mo. |
| De Curtis, 2001 (45) | LS; 27 healthy, term, AGA infants (not defined). Liege, Belgium. | DXA. 3-compartment model was used (FM, FFM, and bone mass) with age-specific values (51).<br>Blinding not stated. | BF: 13<br>FF: 14 | Birth<br>2 mo | BF: exclusively BF.<br>FF: exclusively FF (69 kcal energy, 1.4 g protein, 3.7 g fat, and 7.5 g lactose/dL). |
| Ng, 2004 (44) | LS; term infants. Singapore. | Deuterium dilution. 2-compartment model; age-specific hydration factors for FFM were used (not referenced). Blinding not stated. | BF: 63<br>FF: 37 | 3 mo<br>6 mo<br>12 mo | BF: exclusively BF up to 2 mo of age. FF: predominantly or exclusively FF. Solids introduced significantly later in BF than in FF infants. BF assessment not stated. |
| Modi, 2006 (20) | LS; healthy, term, AGA. Single hospital, London, United Kingdom. Adjusted data presented in article.<br>Additional unadjusted data obtained from authors. | Whole-body MRI. 2-component model. AT volume measured and converted to FM (AT mass in kilograms = AT in liters × 0.9; FM in kilograms = AT mass in kilograms × 0.45) by using age specific values. Blinding not stated. | BF: 9<br>FF: 6 | 6 wk | BF: exclusively BF.<br>FF: exclusively FF. |

(*Continued*)

**TABLE 1** (*Continued*)

| First author, year (reference) | Population and study detail and how recruited | Body-composition technique used, compartment measured, model used, adjusted for infancy (yes or no), reference used for adjustment, and blinded assessment (yes or no) | Study groups: no. of infants | Age at body-composition measurement | Breastfeeding definition, prospective or retrospective data, type of formula |
|---|---|---|---|---|---|
| Chomtho, 2009 (41) | CSS; healthy, term. Single city, Cambridge, United Kingdom. Additional data obtained from authors. | Deuterium dilution. 2 compartment model, age-specific hydration factors for FFM used from Fomon et al (3), using age-specific values. Blinding not stated. | BF 41<br>FF 83 | 12 wk | Combination of 3 cohorts, 1989–1994. BF: predominantly BF. |
| Anderson, 2009 (16) | LS; healthy, term, >2500-g birth-weight infants, single unit, Georgia, USA. Additional data obtained from authors. | ADP. 2-compartment model. Calculations by using FFM constants from Fomon et al (3) and age-specific values. Blinding not stated. | BF 27<br>FF 13 | 2 wk<br>4 wk<br>8 wk<br>12 wk | Breastfeeding assessed prospectively. BF: exclusively BF up to 12 wk of age. FF: received mixed feeds: all infants commenced receiving formula on day 1; 10–100% of feeds were non–breast milk across the study period. |
| Ay, 2010 (43) | LS; 298 infants randomly selected from the Generation R study (prospective cohort of 1232 Dutch mother-infant pairs representative of local population), 252/298 measured at 6 mo. Dutch ethnicity only. | DXA. 2-compartment model. Calculations performed by using age-specific values (52). Blinding not stated. | 252 infants | 6 mo | BF data collected prospectively at 2 and 6 mo of age. BF defined as any breastfeeding at 2 or 6 mo of age. |
| Carberry, 2010 (18) | LS; 77 healthy, term infants, not SGA (>10th centile), maternal BMI (in kg/m$^2$) 18.5–25. 69% follow up by 4.5 mo. Single hospital, Australia. | ADP. 2-compartment model. Calculations by using density measurements from Fomon et al (3) and age-specific values. Blinding not stated. | BF: 30<br>FF: 20 | Birth<br>4.5 mo | BF assessed prospectively. BF: exclusively or predominantly BF at 4.5 mo of age. |
| Eriksson, 2010 (42) | LS; healthy, term, singleton infants. Single city, Sweden. Additional data obtained from authors. | ADP. 2-compartment model. Calculations by using density measurements from Fomon et al (3) and age-specific values. Blinding not stated. | BF: 92<br>FF: 3<br>BF: 85<br>FF: 7 | 10 d<br><br>12 wk | BF assessed prospectively. BF: exclusive BF. Prepregnancy BMI (in kg/m$^2$): 25–29.9 in 22% of women and >30 in 5% of women; 5% of women smoked during pregnancy. |

[1] ADP, air-displacement plethysmography; AGA, appropriate for gestational age; AT, adipose tissue; BCM, body cell mass; BF, breastfed; BM, breast milk; BMC, bone mineral content; CSS, cross-sectional study; DXA, dual-energy X-ray absorptiometry; ECW, extracellular water; FF, formula-fed; FFES, fat-free extracellular solid; FFM, fat-free mass; FM, fat mass; LS, longitudinal study; SGA, small for gestational age; TBK, total-body potassium determination; TBM, total body mass; TBW, total body water; TOBEC, total-body electrical conductivity.

**TABLE 2**
Summary table of body-composition data from individual studies included in the systematic review[1]

| First author, year (reference), and study groups: no. of infants | Age | Fat mass BF | Fat mass FF | Fat-free mass BF | Fat-free mass FF | Percentage of fat mass BF | Percentage of fat mass FF |
|---|---|---|---|---|---|---|---|
| | | kg | kg | kg | kg | % | % |
| Shepherd, 1988 (47) | | | | | | | |
| BF: 34 (16 boys); FF: 48 (20 boys) | | Author contacted; no additional data available | | | | | |
| | | | | | | Boys | Boys |
| | 10 d | — | — | — | — | 11 | 9 |
| | 3 mo | | | | | 29 | 31 |
| | | | | | | Girls | Girls |
| | 10 d | — | — | — | — | 8 | 8 |
| | 3 mo | | | | | 35 | 31 |
| | | | | | | Pooled | Pooled |
| | 10 d | — | — | — | — | 9.4 | 8.4 |
| | 3 mo | | | | | 32.2 | 31 |
| Butte, 1995 (46) | | | | | | | |
| Dilution | Dilution | | | | | | |
| BF: 8; FF: 10 | 1 mo | 0.70 ± 0.28[2] | 0.79 ± 0.09 | 3.86 ± 0.52 | 3.76 ± 0.24 | 15.1 ± 4.4 | 17.4 ± 1.8 |
| TOBEC | TOBEC | | | | | | |
| BF: 9; FF: 10 | 1 mo | 0.81 ± 0.30 | 0.89 ± 0.18 | 3.71 ± 0.44 | 3.67 ± 0.17 | 17.6 ± 4.7 | 19.4 ± 3.3 |
| Dilution | Dilution | | | | | | |
| BF: 10; FF: 10 | 4 mo | 1.97 ± 0.40 | 1.70 ± 0.55 | 4.55 ± 0.47 | 4.74 ± 0.427 | 30.1 ± 4.4 | 26.1 ± 6.5 |
| TOBEC | TOBEC | | | | | | |
| BF: 10; FF: 10 | 4 mo | 1.94 ± 0.36 | 1.67 ± 0.38 | 4.58 ± 0.41 | 4.78 ± 0.34 | 29.6 ± 3.4 | 25.6 ± 4.1 |
| Bellu, 1997 (17) | | | | | | | |
| BF: 26; FF: 53 | 12 mo | 2.18 ± 0.47 | 2.76 ± 0.39 | 6.99 ± 0.62 | 7.38 ± 0.59 | 23.76 ± 3.06 | 27.09 ± 2.80 |
| Motil, 1997 (8) | | | | | | | |
| BF: 10 (7 boys) recruited | 6 wk | 1.13 ± 0.32 | 0.97 ± 0.35 | 4.04 ± 0.4 | 3.78 ± 0.36 | 22 ± 4 | 20 ± 6 |
| but 7 measured. | 3 mo | 1.66 ± 0.51 | 1.58 ± 0.34 | 4.66 ± 0.64 | 4.27 ± 0.54 | 26 ± 6 | 27 ± 6 |
| FF: 10 (2 boys) recruited | 18 wk | 2.02 ± 0.58 | 1.99 ± 0.49 | 5.09 ± 0.43 | 4.83 ± 0.5 | 28 ± 5 | 29 ± 6 |
| but 9 measured. | 6 mo | 2.11 ± 0.55 | 2.27 ± 0.47 | 5.78 ± 0.63 | 5.35 ± 0.67 | 26 ± 5 | 30 ± 6 |
| de Bruin, 1998 (7) | | | | | | | |
| BF: 23 (9 boys); FF: 23 (15 boys) | | Boys | Boys | Boys | Boys | Boys | Boys |
| | 1 mo | 0.70 ± 0.20 | 0.68 ± 0.24 | 3.87 ± 0.40 | 3.91 ± 0.36 | 15.2 ± 3.1 | 14.6 ± 4.2 |
| | 2 mo | 1.17 ± 0.40 | 1.05 ± 0.28 | 4.38 ± 0.41 | 4.43 ± 0.39 | 20.6 ± 5.0 | 18.9 ± 3.3 |
| | 4 mo | 1.71 ± 0.51 | 1.65 ± 0.42 | 5.08 ± 0.46 | 5.13 ± 0.39 | 24.7 ± 5.6 | 24.1 ± 3.7 |
| | 8 mo | 2.35 ± 0.42 | 2.21 ± 0.48 | 6.43 ± 0.52 | 6.43 ± 0.47 | 26.7 ± 3.3 | 25.4 ± 3.7 |
| | 12 mo | 2.71 ± 0.31 | 2.45 ± 0.73 | 7.46 ± 0.60 | 7.79 ± 0.64 | 26.6 ± 1.9 | 23.7 ± 5.4 |
| | | Girls | Girls | Girls | Girls | Girls | Girls |
| | 1 mo | 0.61 ± 0.20 | 0.60 ± 0.11 | 3.51 ± 0.42 | 3.63 ± 0.34 | 14.4 ± 3.8 | 14.2 ± 2.2 |
| | 2 mo | 0.95 ± 0.24 | 1.03 ± 0.15 | 3.95 ± 0.47 | 4.04 ± 0.36 | 19.1 ± 3.2 | 20.4 ± 2.9 |
| | 4 mo | 1.49 ± 0.28 | 1.80 ± 0.14 | 4.43 ± 0.48 | 4.83 ± 0.42 | 25.0 ± 2.5 | 27.2 ± 1.9 |
| | 8 mo | 2.02 ± 0.32 | 2.33 ± 0.31 | 5.86 ± 0.37 | 6.23 ± 0.53 | 25.5 ± 3.2 | 27.3 ± 3.4 |
| | 12 mo | 2.30 ± 0.34 | 2.62 ± 0.46 | 6.92 ± 0.44 | 7.14 ± 0.55 | 24.9 ± 3.0 | 26.7 ± 3.6 |

*(Continued)*

**TABLE 2** (*Continued*)

| First author, year (reference), and study groups: no. of infants | Age | Fat mass BF | Fat mass FF | Fat-free mass BF | Fat-free mass FF | Percentage of fat mass BF | Percentage of fat mass FF |
|---|---|---|---|---|---|---|---|
| | | Pooled | Pooled | Pooled | Pooled | Pooled | Pooled |
| | 1 mo | 0.65 ± 0.20 | 0.65 ± 0.21 | 3.65 ± 0.41 | 3.81 ± 0.35 | 14.7 ± 3.6 | 14.5 ± 3.7 |
| | 2 mo | 1.04 ± 0.31 | 1.04 ± 0.24 | 4.12 ± 0.45 | 4.29 ± 0.38 | 19.7 ± 4.0 | 19.4 ± 3.2 |
| | 4 mo | 1.58 ± 0.38 | 1.70 ± 0.35 | 4.68 ± 0.47 | 5.03 ± 0.40 | 24.9 ± 4.0 | 25.2 ± 3.2 |
| | 8 mo | 2.15 ± 0.36 | 2.25 ± 0.43 | 6.08 ± 0.43 | 6.36 ± 0.49 | 26.0 ± 3.2 | 26.1 ± 3.6 |
| | 12 mo | 2.46 ± 0.33 | 2.51 ± 0.65 | 7.13 ± 0.51 | 7.56 ± 0.61 | 25.6 ± 2.6 | 24.7 ± 4.9 |
| Jiang, 1998 (23) | | | | | | | |
| BF: 11 (4 boys) | 4 mo | 2.014 ± 0.498 | 1.504 ± 0.364 | 4.948 ± 0.511 | 5.065 ± 0.820 | 28.6 ± 4.0 | 23.0 ± 5.0 |
| FF: 11 (7 boys) | | | | | | | |
| BF: 9 (4 boys) | 6 mo | 1.907 ± 0.398 | 1.827 ± 0.687 | 5.297 ± 0.561 | 5.854 ± 0.385 | 26.4 ± 4.2 | 23.4 ± 6.8 |
| FF:10 (6 boys) | | | | | | | |
| Butte, 2000 (6) | | | | | | | |
| BF: 40 (14 boys) | | | | | | | |
| FF: 36 (19 boys) | | Boys | Boys | Boys | Boys | Boys | Boys |
| | 0.5 mo | 0.51 ± 0.38 | 0.35 ± 0.21 | 3.40 ± 0.41 | 3.38 ± 0.33 | 12.76 ± 8.8 | 9.09 ± 4.9 |
| | 3 mo | 2.03 ± 0.37 | 1.77 ± 0.37 | 4.34 ± 0.35 | 4.41 ± 0.52 | 31.73 ± 3.5 | 28.46 ± 3.8 |
| | 6 mo | 2.56 ± 0.45 | 2.04 ± 0.41 | 5.63 ± 0.51 | 5.62 ± 0.72 | 31.14 ± 3.9 | 26.62 ± 4.6 |
| | 9 mo | 2.54 ± 0.59 | 2.02 ± 0.49 | 6.54 ± 0.55 | 6.82 ± 0.76 | 27.75 ± 4.8 | 22.79 ± 4.4 |
| | 12 mo | 2.59 ± 0.61 | 2.53 ± 0.64 | 7.55 ± 0.78 | 7.19 ± 0.67 | 25.38 ± 3.8 | 25.82 ± 4.4 |
| | | Girls | Girls | Girls | Girls | Girls | Girls |
| | 0.5 mo | 0.40 ± 0.23 | 0.52 ± 0.21 | 3.25 ± 0.32 | 3.17 ± 0.35 | 10.51 ± 4.9 | 13.97 ± 5.3 |
| | 3 mo | 1.95 ± 0.43 | 1.82 ± 0.38 | 4.05 ± 0.53 | 4.22 ± 0.37 | 32.49 ± 6.2 | 29.98 ± 4.3 |
| | 6 mo | 2.44 ± 0.44 | 2.47 ± 0.32 | 5.09 ± 0.47 | 5.42 ± 0.71 | 32.31 ± 4.4 | 31.46 ± 4.4 |
| | 9 mo | 2.34 ± 0.40 | 2.78 ± 0.46 | 6.08 ± 0.63 | 6.23 ± 0.75 | 27.82 ± 4.6 | 30.9 ± 5.3 |
| | 12 mo | 2.45 ± 0.49 | 2.91 ± 0.45 | 6.78 ± 0.72 | 7.07 ± 0.65 | 26.55 ± 4.7 | 29.11 ± 3.7 |
| | | Pooled | Pooled | Pooled | Pooled | Pooled | Pooled |
| | 0.5 mo | 0.437 ± 0.287 | 0.433 ± 0.210 | 3.303 ± 0.356 | 3.277 ± 0.338 | 11.30 ± .51 | 11.39 ± 5.10 |
| | 3 mo | 1.982 ± 0.412 | 1.795 ± 0.375 | 4.152 ± 0.477 | 4.321 ± 0.456 | 32.22 ± 5.43 | 29.18 ± 4.07 |
| | 6 mo | 2.479 ± 0.440 | 2.246 ± 0.373 | 5.276 ± 0.484 | 5.529 ± 0.716 | 31.90 ± 4.26 | 28.91 ± 4.50 |
| | 9 mo | 2.409 ± 0.474 | 2.379 ± 0.475 | 6.241 ± 0.605 | 6.539 ± 0.754 | 27.80 ± 4.67 | 26.62 ± 4.82 |
| | 12 mo | 2.502 ± 0.532 | 2.708 ± 0.559 | 7.052 ± 0.736 | 7.132 ± 0.660 | 26.14 ± 4.43 | 27.37 ± 4.09 |
| De Curtis, 2001 (45) | | | | | | | |
| BF: 13 | Birth | — | — | — | — | 15.2 | 16.1 |
| FF: 14 | 2 mo | | | | | 24.1 | 26.7 |
| Ng, 2004 (44) | | | | | | | |
| BF: 63 | 3 mo | — | — | — | — | 22 ± 6.5 | 22.7 ± 5.8 |
| FF: 37 | 6 mo | | | | | 22.8 ± 7.4 | 22.2 ± 5.2 |
| | 12 mo | | | | | 18.4 ± 2.9 | 19.1 ± 2.9 |
| Modi, 2006 (20) | | | | | | | |
| BF: 9 | 6 wk | 0.605 ± 0.109 | 0.652 ± 0.113 | 4.171 ± 0.418 | 4.257 ± 0.451 | 12.61 ± 1.38 | 13.23 ± 1.30 |
| FF: 6 | | | | | | | |

(*Continued*)

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**TABLE 2** (*Continued*)

| First author, year (reference), and study groups: no. of infants | Age | Fat mass | | Fat-free mass | | Percentage of fat mass | |
|---|---|---|---|---|---|---|---|
| | | BF | FF | BF | FF | BF | FF |
| Chomtho, 2009 (41) | | | | | | | |
| BF: 41 | 12 wk | 1.43 ± 0.49 | 1.44 ± 0.45 | 4.44 ± 0.49 | 4.41 ± 0.47 | 24.09 ± 6.71 | 24.46 ± 6.36 |
| FF: 83 | | | | | | | |
| Anderson, 2009 (16) | | — | — | — | — | | |
| BF: 27 (15 boys) | 2 wk | | | | | 12.67 ± 4.38 | 12.5 ± 5.19 |
| FF: 13 (7 boys) | 4 wk | | | | | 17.95 ± 5.13 | 17.25 ± 4.06 |
| | 8 wk | | | | | 22.41 ± 5.46 | 20.99 ± 3.58 |
| | 12 wk | | | | | 24.44 ± 5.87 | 23.15 ± 3.83 |
| Ay, 2010 (43) | | | | | | | |
| 252 infants (145 boys) | 6 mo | Breastfeeding at 6 mo had a significant positive association with the total percentage of fat mass and the truncal percentage of fat mass. No association was seen for breastfeeding at 2 mo. | — | — | — | — | — |
| Carberry, 2010 (18) | | | | | | | |
| BF: 30 (15 boys) | Birth | 0.328 ± 0.155 | 0.346 ± 0.150 | 3.008 ± 0.317 | 3.094 ± 0.372 | 9.64 ± 3.94 | 9.77 ± 3.65 |
| FF: 20 (11 boys) | 4.5 mo | 1.973 ± 0.440 | 1.845 ± 0.509 | 5.093 ± 0.576 | 5.390 ± 0.504 | 27.76 ± 4.47 | 25.2 ± 5.24 |
| Eriksson, 2010 (42) | | | | | | | |
| BF: 92 | 10 d | 0.487 ± 0.189 | 0.561 ± 0.219 | 3.153 ± 0.374 | 3.307 ± 0.353 | 13.02 ± 3.97 | 14.17 ± 3.43 |
| FF: 3 | | | | | | | |
| BF: 85 | 12 wk | 1.67 ± 0.4 | 1.591 ± 0.426 | 4.517 ± 0.418 | 4.519 ± 0.567 | 26.75 ± 4.50 | 25.69 ± 4.29 |
| FF: 7 | | | | | | | |

[1] BF, breastfed; FF, formula-fed; TOBEC, total-body electrical conductivity.
[2] Mean ± SD (all such values).

**TABLE 3**
Mean difference in fat mass between FF and BF infants[1]

| Postnatal age | References | No. of participants | Statistical method | Difference in fat mass[2] | P | Heterogeneity $I^2$ | Heterogeneity P |
|---|---|---|---|---|---|---|---|
| | | | | *kg* | | % | |
| 1–2 mo | 7, 8, 20, 46 | 95 (BF: 47; FF: 48) | Fixed effects | 0.03 (−0.06, 0.11) | 0.49 | 0 | 0.61 |
| 3–4 mo | 6–8, 18, 23, 41, 42, 46 | 446 (BF: 247; FF: 199) | Fixed effects | −0.09 (−0.18, −0.01) | 0.04 | 44 | 0.08 |
| 6 mo | 6, 8, 23 | 115 (BF: 56; FF: 55) | Fixed effects | −0.18 (−0.34, −0.01) | 0.03 | 8 | 0.34 |
| 8–9 mo | 6, 7 | 122 (BF: 63; FF: 59) | Fixed effects | 0.03 (−0.13, 0.19) | 0.70 | 0 | 0.42 |
| 12 mo | 6, 7, 17 | 201 (BF: 89; FF: 112) | Random effects | 0.29 (−0.03, 0.61) | 0.07 | 80 | 0.007 |

[1] BF, breastfed; FF, formula-fed.
[2] All values are means; 95% CIs in parentheses.

asymmetry. There was no evidence of funnel-plot asymmetry for analyses at other time points (*see* Figures 6 and 8–10 under "Supplemental data" in the online issue), although the small number of studies made this difficult to evaluate reliably.

## Pooled differences over the first 12 mo

Pooled differences in fat mass, fat-free mass, and the percentage of fat mass between the formula-fed and breastfed infants by postnatal age are shown in **Figures 2**, **3**, and **4**, respectively.

## Meta-analysis of results measured by using a single technique

Body composition was measured by using the same technique in ≥3 studies at 3–4 and 6 mo only. At 3–4 mo, ADP was used to measure the percentage of fat mass in 3 studies (16, 18, 42); meta-analysis showed a significant reduction in the percentage of fat mass [mean difference (95% CI): −1.72% (−3.47%, 0.03%) ($P$ = 0.05); fixed effects, heterogeneity $I^2$ = 0%, $P$ = 0.75) in formula-fed compared with breastfed infants (*see* Figure 11 under "Supplemental data" in the online issue). At 3–4 mo, 5 studies that used isotope dilution reported results for the percentage of fat mass (8, 23, 41, 44, 46), and 4 studies that used isotope dilution reported results for fat mass and fat-free mass (8, 23, 41, 46). Meta-analysis revealed no significant differences for the percentage of fat mass [−1.36% (−3.98%, 1.25%) ($P$ = 0.31); random effects, heterogeneity $I^2$ = 61%, $P$ = 0.04; *see* Figure 12 under "Supplemental data" in the online issue], fat mass [−0.11 kg (−0.25, 0.03) ($P$ = 0.13); fixed effects, heterogeneity $I^2$ = 57%, $P$ = 0.07; *see* Figure 13 under "Supplemental data" in the online issue], fat-free mass [−0.01 kg (−0.16, 0.14 kg) ($P$ = 0.89); fixed effects, heterogeneity $I^2$ = 0%, $P$ = 0.42; *see* Figure 14 under "Supplemental data" in the online issue]. At 6 mo, by using isotope dilution, 3 studies reported results for the percentage of fat mass (8, 23, 44); the meta-analysis of these studies showed no significant difference [−0.33% (−2.39%, 1.72%) ($P$ = 0.75); fixed effects, heterogeneity $I^2$ = 45%, $P$ = 0.16; *see* Figure 15 under "Supplemental data" in the online issue].

## Sex-specific effects on body composition

Studies that reported body composition by sex are summarized in Table 1. Only 2 studies provided comparable data; De Bruin et al (7) reported data at 1, 2, 4, 8, and 12 mo, and Butte et al (6) report data at 0.5, 3, 6, 9, and 12 mo. We combined these studies by using meta-regression to examine sex differences at 0.5–1, 3–4, 8–9, and 12 mo so that each cohort only contributed to each time point once. There was no evidence of a significant sex difference from the meta-regression at any time point.

## DISCUSSION

In this systematic review and meta-analysis that included 15 studies and >1000 infants, we identified significant differences in body composition between healthy, term breastfed and formula-fed infants ≤1 y of age. We showed that formula-fed infants had higher fat-free mass throughout the first year of life than did breastfed infants but changes in fat mass over this period were more complex. Formula-fed infants had lower fat mass than did their breastfed counterparts at 3–4 and 6 mo. By 12 mo, this effect was no longer apparent, with a trend toward reversal and higher fat mass in formula-fed infants. These findings are biologically plausible. Circulating leptin is higher in

**TABLE 4**
Mean difference in fat-free mass between FF and BF infants[1]

| Postnatal age | References | No. of participants | Statistical method | Difference in fat-free mass[2] | P | Heterogeneity $I^2$ | Heterogeneity P |
|---|---|---|---|---|---|---|---|
| | | | | *kg* | | % | |
| 1–2 mo | 7, 8, 20, 46 | 95 (BF: 47; FF: 48) | Fixed effects | 0.03 (−0.13, 0.19) | 0.85 | 21 | 0.28 |
| 3–4 mo | 6-8, 18, 23, 41, 42, 46 | 446 (BF: 247; FF: 199) | Fixed effects | 0.13 (0.03, 0.23) | 0.01 | 35 | 0.15 |
| 6 mo | 6, 8, 23 | 111 (BF: 56; FF: 55) | Random effects | 0.19 (−0.25, 0.63) | 0.48 | 68 | 0.04 |
| 8–9 mo | 6, 7 | 122 (BF: 63; FF:59) | Fixed effects | 0.29 (0.09, 0.49) | 0.005 | 0 | 0.93 |
| 12 mo | 6, 7, 17 | 201 (BF: 89; FF: 112) | Fixed effects | 0.30 (0.13, 0.48) | 0.0008 | 31 | 0.24 |

[1] BF, breastfed; FF, formula-fed.
[2] All values are means; 95% CIs in parentheses.

**TABLE 5**
Mean difference in the percentage of fat mass between FF and BF infants[1]

| Postnatal age | References | No. of participants | Statistical method | Difference in fat mass[2] | *P* | Heterogeneity $I^2$ | Heterogeneity *P* |
|---|---|---|---|---|---|---|---|
| | | | | | | % | |
| 1–2 mo | 7, 8, 16, 20, 46 | 135 (BF: 74; FF: 61) | Fixed effects | 0.21 (−0.78, 1.21) | 0.67 | 5 | 0.38 |
| 3–4 mo | 6-8, 16, 18, 23, 41, 42, 44, 46 | 586 (BF: 337; FF: 249) | Random effects | −1.46 (−2.75, −0.17) | 0.03 | 50 | 0.04 |
| 6 mo | 6, 8, 23, 44 | 211 (BF: 119; FF: 92) | Fixed effects | −1.71 (−3.14, −0.29) | 0.02 | 57 | 0.07 |
| 8–9 mo | 6, 7 | 122 (BF: 63; FF: 59) | Fixed effects | −0.49 (−1.94, 0.96) | 0.51 | 0 | 0.39 |
| 12 mo | 6, 7, 17, 44 | 301 (BF: 152; FF: 149) | Random effects | 1.21 (−0.46, 2.87) | 0.16 | 76 | 0.005 |

[1] BF, breastfed; FF, formula fed.
[2] All values are means; 95% CIs in parentheses.

breastfed infants than in formula-fed infants ≤4 mo of age but not later in infancy (53) in keeping with the greater fat mass in breastfed infants at 3–4 and 6 mo but not at 12 mo. In addition, greater protein intake (54) and higher resting energy expenditure (8) in infancy have been well described in formula-fed compared with breastfed infants, which are consistent with our finding of higher fat-free mass in the formula-fed group throughout this period. Although we showed no evidence of a difference in effect between boys and girls, this absence may reflect a lack of power because only 2 studies reported sex-specific results. The variance in difference between feeding groups in fat and fat-free mass was most marked at 6 mo. We considered the possibility that this might have been attributable to data from Motil et al (8). Ten breastfed (7 boys) and 10 formula-fed (2 boys) infants were recruited in this study, but body-composition data were provided for only 16 infants (sex distribution was not provided). However, the exclusion of these data did not alter the direction of results.

Our meta-analysis was based on studies that used different methods to assess infant body composition. The extent to which these methods are comparable must be considered. Butte et al (55) showed significant differences in fat mass estimated by using TOBEC, TBK, DXA, and $^2H_2O$ isotope dilution. However, there was no evidence of nonsystematic variation (55), which supported the validity of our analysis that examined the difference in body composition between feeding groups rather than the absolute body composition. In addition, we attempted to address this issue by performing subgroup analyses of studies that reported values measured by using the same technique at a comparable postnatal age. Sufficient studies (≥3 studies) were only available for a minority of time points. In 4 of 5 cases in which this subgroup analysis was possible, we showed differences of the same magnitude and direction as the analyses in which methods were combined. This result supported our analysis of results obtained by using different in vivo body-composition–measurement techniques.

A major limitation of body-composition studies that use indirect techniques in pediatric populations is the rapid maturation of body tissues during childhood (3). Thus, the assumptions inherent in the derivation of fat or fat-free mass may not be stable throughout childhood. Therefore, it is reassuring that all studies included in our meta-analysis used reference standards that are appropriate for infants. Significant differences in body composition exist in relation to sex in adults (56). Although differences in infancy appear less pronounced (57), we intended to examine the effect of sex but were unable to do so because of the limited number of studies that reported outcomes by sex. Studies of infant feeding are liable to important study-level biases such as recall bias if breastfeeding is assessed retrospectively (58), and contamination bias related to formula feeding in the breastfeeding

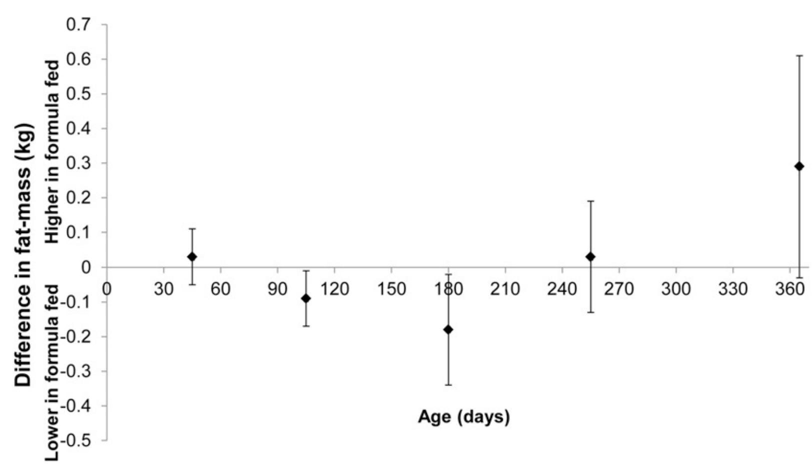


**FIGURE 2.** Pooled mean differences and 95% CIs for fat mass (kg) between formula-fed and breastfed infants by age. A fixed-effects meta-analysis was undertaken with RevMan 5 software (The Cochrane Collaboration) by using the inverse-variance method. This analysis was performed separately for each postnatal age point. When heterogeneity was present ($P < 0.05$; chi-square test), a random-effects meta-analysis was carried out. The meta-analysis technique used, *P* value, and number of subjects at each point were as follows: 1–2 mo: fixed effects, $P = 0.49$, $n = 95$; 3–4 mo: fixed effects, $P = 0.04$, $n = 446$; 6 mo: fixed effects, $P = 0.03$, $n = 111$; 8–9 mo: fixed effects, $P = 0.70$, $n = 122$; and 12 mo: random effects, $P = 0.07$, $n = 112$.

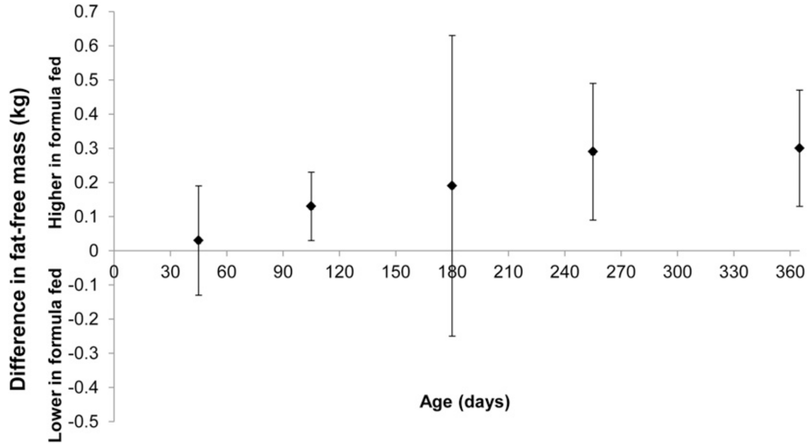


**FIGURE 3.** Pooled mean differences and 95% CIs for fat-free mass (kg) between formula-fed and breastfed infants by age. A fixed-effects meta-analysis was undertaken with RevMan 5 software (The Cochrane Collaboration) by using the inverse-variance method. This analysis was performed separately for each postnatal age point. When heterogeneity was present ($P < 0.05$; chi-square test), a random-effects meta-analysis was carried out. The meta-analysis technique used, $P$ value, and number of subjects at each point were as follows: 1–2 mo: fixed effects, $P = 0.85$, $n = 95$; 3–4 mo: fixed effects, $P = 0.01$, $n = 446$; 6 mo: random effects, $P = 0.48$, $n = 111$; 8–9 mo: fixed effects, $P = 0.005$, $n = 122$; and 12 mo: fixed effects, $P = 0.0008$, $n = 112$.





group. With a single exception (17), breastfeeding was assessed prospectively in all included studies, which limited the recall bias; however, the definition of feeding groups varied widely, and no study reported the use of WHO criteria for exclusive breastfeeding, which suggested that a contamination bias may represent an important source of heterogeneity. The choice of infant feeding is also subject to a number of important confounding influences, such as prematurity and maternal diabetes, that may also affect body composition. We attempted to limit this possibility through the use of strict inclusion criteria. An additional issue was that the limited number of studies at time points other than 3–4 mo would have resulted in limited power to detect important differences. This issue was of particular relevance at 12 mo, at which, in contrast to our findings at 3–4 mo, there was a suggestion that formula-fed infants had higher fat mass than did infants who were breastfed. Finally, the use of the percentage of fat mass as a proxy for adiposity in body-composition studies has been criticized for methodologic and statistical reasons (59, 60); thus, we included measures of fat and fat-free mass as well as the percentage of fat mass. The representation of fat mass by using alternatives such as a fat-mass index to adjust for body size (59) has been recommended, but we were unable to include such an alternative in our analyses because such data were only available in 3 articles (20, 41, 42) and were not at assessed at comparable time points.

To our knowledge, the pattern of body-composition development over the first year of life that we identified is a novel finding that raises intriguing hypotheses in relation to possible evolutionary drivers and causal biological mechanisms. Key differences exist in macronutrient content and bioactive factors between breast milk and formula. The protein content of formula is higher than that of pooled breast-milk reference samples. However, a hallmark of breast milk is that composition varies widely between mothers and within mothers across feeds by time of day and duration of lactation (61) and even between different mammary lobes within the same breast (62). Differences also

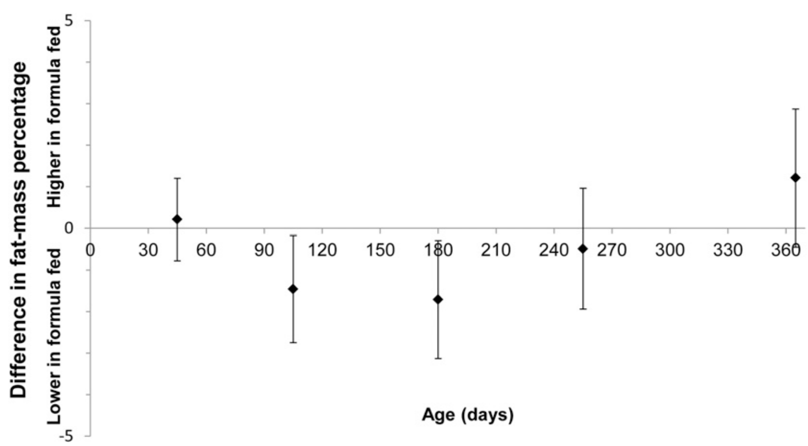


**FIGURE 4.** Pooled mean differences and 95% CIs for the percentage of fat mass between formula-fed and breastfed infants by age. A fixed-effects meta-analysis was undertaken with RevMan 5 software (The Cochrane Collaboration) by using the inverse-variance method. This analysis was performed separately for each postnatal age point. When heterogeneity was present ($P < 0.05$; chi-square test), a random effects meta-analysis was carried out. The meta-analysis technique used, $P$ value, and number of subjects at each point were as follows: 1–2 mo: fixed effects, $P = 0.67$, $n = 135$; 3–4 mo: random effects, $P = 0.03$, $n = 586$; 6 mo: fixed effects, $P = 0.02$, $n = 211$; 8–9 mo: fixed effects, $P = 0.51$, $n = 122$; and 12 mo: random effects, $P = 0.16$, $n = 301$.

exist in feeding behaviors between suckled and bottle-fed infants because suckled infants are more likely to initiate and terminate feeding sessions (63). Because infants who freely suckled at the breast appear to self-regulate intake (64), this effect raises the important question of the true extent to which macronutrient intake differs from that of formula-fed infants. The large number of potentially bioactive hormones (65), proteins (66), cytokines (67), and growth factors (68) in breast milk add additional dimensions to differences far beyond those attributable to the macronutrient content.

The higher fat-free mass seen in association with formula feeding is of note. Fat-free mass reflects a heterogeneous group of tissues including bone, muscle, organs, and connective tissue, and hence, the biological implications are uncertain. Future work should aim to distinguish the specific components of fat-free mass influenced by infant feeding. The higher fat mass in early infancy that we showed to be associated with breastfeeding, which is replicated across mammalian species (69), can be assumed to represent an evolutionary mechanism to support the infant during the precarious weaning period. If we accept the presumption that breast milk represents the ideal nutrition for infants, our finding that formula-fed infants are insufficiently adipose in the preweaning period suggests that infant formulas are not supporting the normal trajectory of adipose tissue development. The apparent switch from higher adiposity in breastfed infants at 3–4 mo to greater adiposity in formula-fed infants at 12 mo would also support the possibility of a programming effect of early infant feeding on intermediary metabolism or appetite regulation. Research involving animal models showed that subtle changes in early feed composition led to alterations in adiposity that preceded deranged glucose metabolism (70). Accumulating evidence from long-term cohort studies indicates that body composition in childhood tracks into adult life (71). The data presented in the current study suggest that initiating events may well arise earlier in infancy and result from early feeding choices. Although the differences in fat mass we described are small (of the order of 90 g at 3–4 mo of age and 180 g at 6 mo of age), our findings add to the developing understanding of the possible contributions of breastfeeding and formula feeding on risk of obesity in childhood and adult life. What is now required is long-term follow-up of adequately powered cohorts to identify the outcomes associated with these early differences.

We acknowledge all authors who contributed data to this meta-analysis.

The authors' responsibilities were as follows—CG: initiated and designed the study; CG, KML, JRCP, and MJH: conducted the literature review; CG and SS: analyzed data; CG and NM: discussed the study and wrote, revised, and prepared drafts of the manuscript, including the final version of the manuscript; NM: had primary responsibility for the final content of the manuscript; and all authors: read, revised, and approved the final manuscript. CG has received support from Pfizer Nutrition to attend an educational conference, but declared no other conflict of interest. MJH has received support from Danone International to attend an educational conference, but declared no other conflict of interest. NM has received consultancy fees from Ferring Pharmaceuticals, but declared no other conflict of interest. KML, SS, and JRCP declared no conflicts of interest.

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