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Adiposity and hepatic lipid in healthy full-term, breastfed, and formula-fed human infants: a prospective short-term longitudinal cohort study[1–3]

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ABSTRACT

Background: The effect of mode of infant feeding on adiposity deposition is not fully understood.

Objective: The objective was to test the hypothesis that differences in total and regional adipose tissue content and intrahepatocellular lipid (IHCL) arise in early infancy between breast- and formula-fed infants and to describe longitudinal changes.

Design: This prospective longitudinal cohort study was performed in 2 hospitals in the United Kingdom. Healthy, full-term, appropriate weight-for-gestational age infants were recruited; adipose tissue volume and distribution were directly quantified by using whole-body magnetic resonance imaging; IHCL was assessed by in vivo proton magnetic resonance spectroscopy. Measurements were performed after birth (median age: 13 d) and at 6–12 wk of age. Method of infant feeding was recorded prospectively by using maternally completed feeding diaries. *Breastfed* was defined as >80% of feeds consisting of breast milk at both points; *formula-fed* was defined as >80% of feeds consisting of formula milk at both points.

Results: Longitudinal results were obtained from 70 infants (36 breastfed, 9 mixed-fed, and 25 formula-fed). No differences were found in total or regional adipose tissue or IHCL between breastfed and formula-fed infants. In pooled analyses including all feeding groups, IHCL and total adipose tissue approximately doubled between birth and 6–12 wk: IHCL after birth (median: 0.949; IQR: 0.521–1.711) and at 6–12 wk (1.828; 1.376–2.697; $P < 0.001$) and total adipose tissue after birth (0.749 L; 0.620–0.928 L) and at 6–12 wk (1.547 L; 1.332–1.790 L; $P < 0.001$). Increasing adiposity was characterized by greater relative increases in subcutaneous than in internal adipose tissue depots.

Conclusions: No differences were detectable in adipose tissue or IHCL accretion between breastfed and formula-fed infants up to 2 mo. The substantial increase in IHCL seen over this period in both breastfed and formula-fed infants is a novel observation, which suggests that hepatic storage of lipids may be physiologic up to 2 mo. This trial was registered at www.clinicaltrials.gov as NCT02033005. *Am J Clin Nutr* 2014;99:1034–40.

INTRODUCTION

Breastfeeding is considered the optimal diet for the human infant. When compared with formula feeding, breastfeeding has been associated with many health benefits (1, 2). An area that remains contentious is the potential protective long-term effect of breastfeeding on adiposity and the development of later obesity. Numerous observational studies have described associations between breastfeeding and lower rates of later obesity (3–5); however, these may be a consequence of confounding by factors such as socioeconomic class and maternal BMI (6, 7).

Patterns of growth (8) and body composition (9) differ between formula and breastfed infants, with increasing deviation seen between 6 mo and 1 y. Therefore, if breastfeeding does have a positive effect on reducing later obesity, a plausible mediating pathway may be through changes in the amount and distribution of adipose tissue laid down in infancy as adiposity tracks from infancy into adulthood (10). Previous studies that examined infant adiposity in relation to feeding have been inconclusive and limited by small sample sizes, cross-sectional designs, heterogeneity of infant feeding, and indirect measures of body adiposity (11, 12). We previously developed the application of whole-body MRI to quantify total and regional adipose tissue depots directly in newborns (13, 14). We have also used in vivo magnetic resonance spectroscopy (MRS)[4] to quantify intrahepatocellular lipid (IHCL) deposition in preterm and term neonates (15, 16). Although an association between breastfeeding in infancy and fatty liver in later childhood has been reported (17), to our knowledge no data describing longitudinal changes in IHCL in early life or in relation to infant feeding have been published.

We aimed to test the null hypothesis that no differences in total and regional adiposity and IHCL deposition in early infancy

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[4] Abbreviations used: IA, internal abdominal; IHCL, intrahepatocellular lipid; MRS, magnetic resonance spectroscopy; SCA, total subcutaneous abdominal.

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(up to 2–3 mo) exist between breastfed, mixed-fed, and formula-fed infants. In addition, we aimed to provide longitudinal data on these measures in healthy, full-term human infants over the same period.

SUBJECTS AND METHODS

Participants consisted of infants from 2 cohorts with longitudinal measures taken at 2 points: baseline (median age: 13 d) and follow-up (6–12 wk). The first cohort consisted of healthy, full term, appropriate weight-for-gestational age infants recruited between November 1999 and October 2001 at the Hammersmith Hospital, London, United Kingdom, and was described previously (18). The second cohort consisted of healthy, full-term, appropriate weight-for-gestational age infants recruited between March 2010 and May 2012 from the postnatal ward at Chelsea and Westminster Hospital, London, United Kingdom.

In both cohorts, infants of diabetic mothers and mothers who smoked—factors known to influence breast milk composition (19, 20)—were excluded. Information on infant feeding was recorded prospectively by using a parent-completed feed diary and was categorized as exclusively/predominantly breastfed (>80% of feeds consisting of breast milk), exclusively/predominantly formula-fed (>80% of feeds consisting of formula milk), or mixed-fed (20–80% of feeds consisting of breast milk) (21). Because we previously showed an association with infant adiposity, we adjusted comparisons for maternal prepregnancy BMI (16). This was determined from prepregnancy weight obtained by maternal recall and maternal height measured at pregnancy booking. Maternal BMI data were not available for infants recruited from the Hammersmith Hospital.

Anthropometric measurements, whole-body MRI measurement of adipose tissue volume, and hepatic MRS to quantify IHCL were performed on infants at baseline and follow-up by using identical techniques in both cohorts. Weight was measured by using scales accurate to 0.2 g (Marsden Professional Baby Scale). Magnetic resonance investigations were performed with infants in natural sleep as previously described (22) at the Robert Steiner Unit, Hammersmith Hospital.

Whole-body MRS images were acquired on a Phillips 1.5 Tesla system by using a T_1-weighted rapid-spin-echo sequence (repetition time of 500 ms, echo time of 17 ms, echo train length of 3) by using a Q body coil. The slice thickness was 5 mm, and the interslice difference was 5 mm. Voxel size was 0.31 × 0.31 × 0.31 cm. Scanning time was approximately 15 min. All MRS images were analyzed independently of the investigators and blind to participant identity and feeding group by VardisGroup (www.vardisgroup.com) by using an image segmentation program (SliceOmatic; Tomovision). Total adipose tissue volume was calculated as the sum of 6 individually quantified adipose tissue compartments: superficial subcutaneous abdominal, superficial subcutaneous nonabdominal, deep subcutaneous abdominal, deep subcutaneous nonabdominal, internal abdominal (IA), and internal nonabdominal, as previously described (23). Total subcutaneous adipose tissue was calculated as the sum of abdominal superficial subcutaneous, abdominal deep subcutaneous, nonabdominal superficial subcutaneous, and nonabdominal deep subcutaneous. Total internal adipose tissue was calculated as the sum of IA and internal nonabdominal. To calculate the ratio of IA to total subcutaneous abdominal (SCA) (IA:SCA), SCA comprised superficial subcutaneous abdominal and deep subcutaneous abdominal compartments.

Proton magnetic resonance spectra were acquired from infants recruited at Chelsea and Westminster Hospital at 1.5T from the right lobe of the liver by using a point-resolved spectroscopy sequence (24), a repetition time of 1500 ms, and an echo time of 135 ms without water saturation and with 128 signal averages. Transverse images of the liver were used to ensure accurate positioning of the (20 × 20 × 20 mm) voxel in the liver, avoiding blood vessels, the gall bladder, and fatty tissue. Spectra were analyzed in the time domain with the AMARES algorithm included in the MRUI software package (25, 26) by a single investigator (ELT) who was blind to the feeding category. Peak areas for all resonances were obtained, and lipid resonances were quantified with reference to water resonance after correction for T_1 and T_2 (27). Hepatic water, known to be relatively constant (28), was used as an internal standard, and the results are presented as the ratio of IHCL CH_2 to water. Percentage adipose tissue was calculated as previously described (13). The study received approval by the National Research Ethics Committee (REC reference 10/H0713/5).

Statistical analyses

The analyses were performed by using SPSS version 20. Statistical significance was defined as $P < 0.05$. Normality was assessed by using the Shapiro-Wilk test (29). When data were not normally distributed ($P < 0.05$ from the Shapiro-Wilk test), a natural log transformation was undertaken. When data remained nonnormal in distribution, nonparametric tests were used.

To compare demographic factors, total and regional adiposity, and IHCL between feeding groups, 1-factor ANOVA for normal data or Kruskal-Wallis 1-factor ANOVA tests for nonnormal data were used separately for baseline and follow-up.

We examined whether change in adiposity between baseline and follow-up differed by feeding group. Multivariable regression was used to examine the outcome (total or regional adipose tissue volumes at follow-up) after adjustment for the same adipose tissue compartment (or total adipose tissue) at baseline, with formula-fed and mixed-fed groups compared with breastfed infants. Adjustment was made for sex, maternal BMI, and weight at follow-up, because these factors are associated with infant adiposity. Because age at baseline was both variable and associated with body size at baseline (and therefore adiposity), sensitivity analyses were carried out with adjustment for a measure of relative adiposity at baseline (percentage body mass consisting of adipose tissue) instead of adipose compartment volume at baseline. For the calculation of percentage adiposity, adipose tissue volume was converted to adipose tissue mass by using the following formula: adipose tissue mass = adipose tissue volume × 0.90 (13). To check for violation of regression assumptions, standardized residuals were assessed for normality.

We described longitudinal changes in adiposity and IHCL combining data if no differences were found between feeding groups. To account for variation in postnatal age at baseline and follow-up in longitudinal comparisons, total and regional adiposity data were standardized (assuming an infant-specific linear relation with age between baseline and follow-up) to the median

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postnatal age at each scan. Because the linearity of the relation between IHCL and postnatal age is unknown, these data were not standardized. Longitudinal changes in adipose tissue volumes and IHCL between baseline and follow-up were examined by using the related-sample *t* test or related-samples Wilcoxon's signed-rank test if data were nonnormal. Correlations between IHCL and adipose tissue volumes were examined by using Spearman's rank correlation.

Because ethnicity is associated with adiposity in infancy (23), sensitivity analyses were undertaken after exclusion of nonwhite infants. An additional sensitivity analysis was undertaken including only exclusively breastfed and exclusively formula fed infants.

Sample size

The study was powered to detect a difference in change in total adipose tissue volume between baseline and follow-up between feeding groups. The only previously published study directly measuring adipose tissue in term infants in relation to method of feeding included 15 infants; this study reported mean (±SD) values for percentage adipose tissue of 26% ± 2.60% among breastfed infants and 27.5% ± 2.37% among formula-fed infants at 6 wk (18). To achieve 80% power (5% significance) to detect a similar magnitude of difference at 12 wk, assuming a correlation of 0.6 between measurements at baseline and follow-up, we estimated that a minimum of 28 infants were required in each of the exclusively/predominantly breastfed and exclusively/predominantly formula-fed groups.

RESULTS

One hundred twenty-four infants were recruited, 16 of whom were from the cohort recruited from the Hammersmith Hospital, details of which were described previously (18), and 108 of whom were from Chelsea and Westminster Hospital. Longitudinal outcome data were available for 54 Chelsea and Westminster infants (38 infants were withdrawn because their parents were unable to attend, 33 before attending the first scan, and 5 between the first and second scans; 16 infants did not settle sufficiently during the MR investigations).

In total, we acquired longitudinal outcome data for 70 infants. At the first scan, 38 infants were fed >80% breast milk, and 25 were fed >80% formula milk; at the second scan, 37 infants were fed >80% breast milk, and 27 were fed >80% formula milk. Therefore, 36 infants (25 boys and 11 girls) were exclusively/predominantly breastfed, 25 were exclusively/predominantly formula-fed at both time points (10 boys and 15 girls), and 9 infants were mixed-fed (5 boys and 4 girls). The infant formulas used included SMA First (Nestle UK Ltd), 12 infants; Aptamil First (Nutricia Ltd), 25 infants; and Cow & Gate First Infant Milk (Nutricia Ltd), 3 infants (some infants were fed more than one formula). Fifty-five infants were of white origin, 12 of mixed origin, one of Asian origin, and 2 of African origin.

Comparisons between breastfed, mixed-fed, and formula-fed infants

All 70 infants were included in these analyses. Anthropometric, adiposity, and IHCL data at baseline and follow-up by feeding group are shown in **Table 1**; no significant differences were detected between feeding groups in anthropometric measures, unadjusted total or regional adipose tissue volumes, or IHCL at baseline or follow-up. After adjustment for adiposity or IHCL at baseline, sex, weight at follow-up, and maternal BMI, no significant differences were detected between feeding groups in total or regional adipose tissue or IHCL (**Table 2**). Sensitivity analyses including only exclusively breastfed (n = 16) and exclusively formula-fed (n = 7) infants did not alter these conclusions. Sensitivity analyses after adjustment for percentage adipose tissue at baseline instead of adiposity at baseline and exclusion of nonwhite infants did not alter these conclusions. No significant differences in the rate of change in total adipose tissue, regional adiposity, or IHCL were found between feeding groups (*see* Supplementary Table 1 under "Supplemental data" in the online issue).

Longitudinal changes in adiposity

Data from all 70 infants were pooled in these analyses. Median age at baseline was 13 d and at follow-up was 63 d; data for total and regional adipose tissue were standardized to these postnatal ages. Total adipose tissue volume approximately doubled between baseline and follow-up (**Table 3**). The magnitude of increase differed between depots; the largest relative change between baseline and follow-up occurred in the superficial subcutaneous abdominal and deep subcutaneous abdominal depots, and proportionally greater increases were seen in superficial subcutaneous abdominal than in internal depots, as evidenced by the significant decrease in the ratio of IA to SCA (IA:SCA) adipose tissue between baseline and follow-up ($P <$ 0.001 from related-samples Wilcoxon's signed-rank test) (Table 3).

Data for IHCL were not standardized to postnatal age. IHCL approximately doubled between baseline (median: 0.949; IQR: 0.521–1.711) and follow-up (median: 1.828; IQR: 1.376–2.697); $P <$ 0.001 from related-samples Wilcoxon's signed-rank test (median percentage change: 113%; IQR: −18% to 284%). No significant correlation was found between IHCL and total adipose tissue or individual adipose tissue depots at baseline or at follow-up (*see* Supplementary Table 2 under "Supplemental data" in the online issue) or between change in total or individual adipose tissue depots and change in IHCL between baseline and follow-up (*see* Supplementary Table 3 under "Supplemental data" in the online issue). Sensitivity analyses after exclusion of nonwhite infants did not alter these conclusions.

DISCUSSION

In this short-term, prospective, longitudinal, cohort study, we identified no significant differences in adipose tissue content or distribution or in IHCL content between healthy breastfed and formula-fed infants at 2 mo. We made the novel observation that over the first 2 postnatal months, there was an approximate doubling of IHCL and that, over this period, adipose tissue accumulation occurred primarily within the subcutaneous depots and that the relative contribution of internal depots to total adiposity diminished. The key strengths of our study were the use of gold standard direct measurement techniques, analyses of

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TABLE 1
Anthropometric data, AT compartment volumes, and IHCL at baseline and follow-up by feeding group[1]

	Baseline			Follow-up		
	Breastfed	Mixed-fed	Formula-fed	Breastfed	Mixed-fed	Formula-fed
Age (d)[2]	13 (9–18)[3]	2 (1–10)	16 (9–20)	63 (58–68)	59 (48–69)	64 (57–74)
Weight (kg)[2]	3.647 ± 0.421[4]	3.332 ± 0.478	3.622 ± 0.595	5.351 ± 0.601	5.317 ± 0.667	5.430 ± 0.696
Length (m)[2]	0.533 ± 0.023	0.510 ± 0.025	0.523 ± 0.025	0.596 ± 0.025	0.582 ± 0.031	0.591 ± 0.029
OFC (cm)[2]	36.5 ± 1.4	35.0 ± 1.7	36.0 ± 1.6	39.8 ± 1.2	38.7 ± 2.1	39.4 ± 1.3
Total AT (L)[5]	0.710 (0.632–0.899)	0.802 (0.620–0.949)	0.722 (0.613–0.913)	1.475 (1.336–1.726)	1.763 (1.450–1.787)	1.505 (1.324–1.930)
Total AT mass (%)[5]	17.5 (16.3–19.8)	21.3 (18.9–22.1)	18.3 (16.6–21.7)	35.6 (32.4–42.9)	47.8 (38.8–48.3)	40.6 (32.4–47.0)
Superficial subcutaneous abdominal AT (L)[5]	0.098 (0.077–0.122)	0.110 (0.090–0.116)	0.103 (0.075–0.14)	0.251 (0.206–0.302)	0.323 (0.250–0.344)	0.264 (0.216–0.324)
Superficial subcutaneous nonabdominal AT (L)[5]	0.512 (0.454–0.680)	0.572 (0.423–0.692)	0.521 (0.452–0.648)	1.078 (0.934–1.209)	1.199 (1.002–1.270)	1.085 (0.926–1.338)
Deep subcutaneous abdominal AT (L)[5]	0.015 (0.011–0.021)	0.013 (0.011–0.024)	0.019 (0.011–0.022)	0.039 (0.030–0.048)	0.044 (0.041–0.057)	0.038 (0.031–0.051)
Deep subcutaneous nonabdominal AT (L)[5]	0.012 (0.009–0.015)	0.012 (0.012–0.014)	0.013 (0.011–0.016)	0.020 (0.016–0.023)	0.023 (0.020–0.026)	0.020 (0.015–0.023)
IA AT (L)[5]	0.017 (0.013–0.022)	0.022 (0.014–0.027)	0.017 (0.012–0.022)	0.028 (0.021–0.036)	0.029 (0.025–0.036)	0.035 (0.24–0.042)
Internal nonabdominal AT (L)[5]	0.054 (0.044–0.065)	0.061 (0.051–0.078)	0.052 (0.047–0.072)	0.086 (0.068–0.115)	0.081 (0.070–0.086)	0.102 (0.076–0.127)
Total subcutaneous AT (L)[5]	0.633 (0.570–0.833)	0.718 (0.484–0.950)	0.654 (0.529–832)	1.351 (1.235–1.598)	1.586 (1.298–1.803)	1.391 (1.184–1.779)
Total internal AT (L)[5]	0.070 (0.056–0.086)	0.084 (0.059–0.106)	0.069 (0.055–0.091)	0.124 (0.096–0.149)	0.109 (0.093–0.142)	0.137 (0.111–0.171)
IA:SCA[5]	0.16 (0.11–0.20)	0.15 (0.11–0.22)	0.14 (0.10–0.17)	0.10 (0.08–0.15)	0.10 (0.07–0.13)	0.11 (0.08–0.14)
IHCL[6,7]	0.662 (0.353–1.965)	1.126 (0.695–1.573)	1.197 (0.710–1.650)	1.846 (1.408–2.429)	0.850 (0.641–2.367)	1.840 (1.388–3.021)

[1] No significant differences were detected between feeding groups at baseline or follow-up from 1-factor ANOVA for normal data or from Kruskal-Wallis 1-factor ANOVA tests for nonnormal data. AT, adipose tissue; IA, internal abdominal; IHCL, intrahepatocellular lipid; OFC, occipitofrontal circumference; SCA, total subcutaneous abdominal.

[2] n = 36, 9, and 25 for breastfed, mixed-fed, and formula-fed infants, respectively.

[3] Median; IQR in parentheses (all such values).

[4] Mean ± SD (all such values).

[5] n = 35, 9, and 24 for breastfed, mixed-fed, and formula-fed infants, respectively.

[6] Ratio of CH_2 to water.

[7] n = 30, 4, and 20 for breastfed, mixed-fed, and formula-fed infants, respectively.

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TABLE 2
Mean difference in adiposity and IHCL at follow-up compared with breastfed infants (adjusted for adiposity or IHCL at baseline, sex, weight at follow-up, and maternal BMI)[1]

	R^2	Formula-fed	Mixed-fed	P^2
Total AT (L)	0.65	−0.057 (−0.234, 0.121)	0.038 (−0.232, 0.308)	0.73
Superficial subcutaneous abdominal AT (L)	0.57	−0.012 (−0.055, 0.032)	0.003 (−0.063, 0.069)	0.84
Superficial subcutaneous nonabdominal AT (L)	0.65	−0.023 (−0.146, 0.100)	0.067 (−0.119, 0.253)	0.64
Deep subcutaneous abdominal AT (L)	0.36	−0.004 (−0.013, 0.05)	0.005 (−0.009, 0.018)	0.38
Deep subcutaneous nonabdominal AT (% difference)	0.40	−14.1 (−34.8, 13.2)	13.3 (−25.4, 72.0)	0.37[3]
IA AT (L)	0.17	0.004 (−0.007, 0.015)	−0.008 (−0.025, 0.008)	0.39
Internal nonabdominal AT (L)	0.29	−0.005 (−0.027, 0.017)	−0.008 (−0.042, 0.025)	0.84
Total subcutaneous AT (L)	0.61	−0.048 (−0.209, 0.113)	0.068 (−0.177, 0.313)	0.63
Total internal AT (L)	0.20	−0.001 (−0.029, 0.031)	−0.018 (−0.061, 0.025)	0.70
IA:SCA	0.18	0.02 (−0.01, 0.04)	−0.02 (−0.06, 0.02)	0.15
IHCL (% difference)[4]	0.23	−13.6 (−51.1, 52.7)	−49.3 (−78.2, 7.6)	0.27[3]

[1] n = 47 (29 breastfed, 4 mixed-fed, and 14 formula-fed); reduced n reflects the lack of maternal BMI data in some infants. Data are means, except where indicated otherwise; 95% CIs in parentheses. AT, adipose tissue; IA, internal abdominal; IHCL, intrahepatocellular lipid; SCA, total subcutaneous abdominal.
[2] Represents significance of the method of feeding in the overall analyses including all feeding groups (from multivariable regression).
[3] From multivariable regression of natural log-transformed data (performed by using transformed data due to nonnormal distribution of residuals).
[4] Ratio of CH_2 to water.

imaging and spectroscopy data blind to feeding category, prospective recording of infant feeding, and broad inclusion criteria supporting the generalizability of results to other healthy infant populations.

IHCL estimated by MRS correlated well with values obtained by liver biopsy (30, 31), and with hepatic steatosis in adult studies (32), and was reproducible and not significantly affected by the fasting state. In older children and adults hepatic lipid is strongly associated with internal adipose tissue depots (33–37), and its accumulation is considered pathological (38, 39). In contrast, in healthy infants up to 2 mo of age, we showed a marked expansion of hepatic lipid concurrent with a relative diminution in internal adipose tissue and a substantial increase in superficial adipose tissue stores. These data corroborate evidence from a previous cross-sectional study in which we suggested that IHCL might increase over the early postnatal period (16). In lean fit adults, IHCL is virtually undetectable (40) and the values we report at 6–12 wk are higher in magnitude than values seen in healthy, lean adults (27, 41). Necropsy studies of stillbirths and neonatal deaths previously showed hepatic lipid accumulation in early infancy, which has been considered indicative of steatosis or pathological deposition (42, 43). We suggest that, in human infants over the first postnatal months, hepatic lipid may represent a physiologic rather than a pathological energy store, similar to that seen in migratory birds before seasonal journeys (44) and in other mammal species before hibernation (45). In early infancy the deposition of lipid in adipose tissue and in the liver, as a readily mobilizable energy source, would agree with evolutionary pressure to safeguard the infant through the period of nutritional insecurity around weaning. Animal data support these findings; hepatic lipoprotein lipase is not expressed in adult humans or animals; however, high concentrations of hepatic lipoprotein lipase have been shown in neonatal rats (46) and mice (47), in which expression parallels hepatic triacylglycerol accumulation and is enhanced during periods of starvation (48). To our knowledge, hepatic lipoprotein lipase expression has not been examined in human infants, but differential expression during development offers a possible explanation for the increase in IHCL that we describe up to 2 mo.

TABLE 3
Total AT volume and AT compartment volumes among the combined cohort, postnatal age at scan standardized to 13 d for baseline and 63 d for follow-up[1]

	Baseline (n = 69)	Follow-up (n = 69)	Change (n = 69)
	L	*L*	%
Total AT	0.749 (0.620–0.928)	1.547 (1.332–1.790)	105 (69–140)
Superficial subcutaneous abdominal AT	0.106 (0.0791–0.132)	0.267 (0.204–0.321)	138 (90–208)
Superficial subcutaneous nonabdominal AT	0.551 (0.445–0.687)	1.066 (0.942–1.277)	101 (63–137)
Deep subcutaneous abdominal AT	0.016 (0.012–0.022)	0.039 (0.031–0.049)	131 (80–196)
Deep subcutaneous nonabdominal AT	0.013 (0.010–0.015)	0.020 (0.016–0.024)	53 (20–98)
Internal abdominal AT	0.019 (0.013–0.026)	0.028 (0.022–0.042)	69 (9–147)
Internal nonabdominal AT	0.053 (0.044–0.069)	0.085 (0.071–0.115)	62 (23–133)
Total subcutaneous AT	0.688 (0.544–0.867)	1.446 (1.210–1.676)	109 (70–148)
Total internal AT	0.074 (0.058–0.096)	0.134 (0.100–0.148)	76 (21–117)
IA:SCA	0.15 (0.11–0.19)[2]	0.10 (0.08–0.14)[2]	—

[1] All values are medians; IQR in parentheses. AT, adipose tissue; IA, internal abdominal; SCA, total subcutaneous abdominal.
[2] $P < 0.001$ from related samples (Wilcoxon's signed-rank test).

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We previously showed in a meta-analysis, in which a variety of body-composition methods were used, that healthy breastfed infants have a higher fat mass than their formula-fed counterparts before weaning (9). We were unable to corroborate this finding in our current study, but we accept that the weaknesses of this study included the limited power to detect subtle differences between breastfed and formula-fed infants, that the use of a cutoff of 80% feeds consisting of breast milk or formula milk to define the feeding groups may not have been sufficiently discriminatory to produce statistical differences between the breastfed and formula-fed groups, and that, although we adjusted for sex, we did not consider it appropriate to run separate analyses for boys and girls because of the small numbers involved. We addressed the variation in postnatal age at baseline and follow-up examinations and the diverse ethnicity of the population through standardization of adiposity for postnatal age and sensitivity analyses. The absence of biochemical measures in our cohort left us unable to comment on whether the hepatic lipid accumulation we described was associated with altered glucose metabolism—a phenomenon well described in adults (34).

An increase in subcutaneous adiposity arising in the preweaning period would be in keeping with evolutionary theory proposing that this substantial energy store promoted the development of the energy-avid, larger human brain (49). We anticipated that IHCL and relative adiposity would decline after weaning, but we were unable to obtain further measurements later in infancy to examine this possibility because MR investigations in later infancy are precluded by the increasing difficulty in keeping older infants settled in natural sleep and our view that it is not ethical to use sedation for exploratory observational studies (22). In light of observational data indicating a protective effect of breastfeeding on progression of nonalcoholic fatty liver disease in childhood (17), the lack of a relation between method of feeding and IHCL or change in IHCL in the first 2 postnatal months is of note and adds further weight to our suggestion that IHCL accumulation in early infancy is a normal developmental phenomenon. Resolution of these uncertainties requires longitudinal follow-up of a larger cohort across infancy and into childhood using noninvasive techniques.

The effect of early postnatal nutrition on later body composition is of considerable interest given the high worldwide prevalence of obesity and the rising mortality and morbidity from obesity-associated chronic noncommunicable diseases (50). Breastfeeding is commonly cited as a means to reduce the risk of later overweight and obesity (51). Several observational studies have identified an association between breastfeeding and reduced risk of later obesity (3–5). However, studies in which the possibility of confounding is more fully addressed, through use of individual patient data to allow for the most accurate treatment of confounding factors in meta-analyses (6) or comparison of populations with different confounding structures (7), have failed to show a significant association. In addition, a cluster randomized controlled trial of the WHO/UNICEF Baby Friendly intervention to promote breastfeeding found no significant effect on overweight or obesity at age 11.5 y (52). These findings cast doubt on the suggested causal effect of breastfeeding on later obesity or overweight. When interpreted in the context of these longer-term studies, our data, although only pertaining to the first few months of life, are of interest because of the failure to detect an effect of formula feeding on adiposity—a proposed mediator of later body composition. It is, however, important to recognize the limited duration of our study. For the reasons discussed above, we were unable to examine adipose tissue content and distribution in later infancy—a period when indirect techniques have detected increasing divergence in body composition between breast and formula-fed populations (9).

In conclusion, we found no evidence to support method of feeding as a factor influencing infant adiposity in the first 2–3 mo of life. Our data do, however, contribute to our understanding of the ontogeny of body composition and energy stores in early infancy.

We are grateful to the many parents who consented to their infants' participation in this study. We acknowledge the inclusion of data from 16 infants recruited by Tracy Harrington for an earlier study.

The authors' responsibilities were as follows—CG, ELT, JDB, and NM: designed the research; CG, SJ, KML, JRCP, SU, and GD: conducted the research; CG, ELT, GD, and SS: analyzed the data; and CG: had primary responsibility for the final content. All authors read and approved the final manuscript and wrote the manuscript. CG received support from Pfizer Nutrition to attend an educational conference; he declared no other conflict of interest. In the past 5 y, NM received consultancy fees from Ferring Pharmaceuticals, speaker honorarium for an educational meeting funded by Nestlé International in which they had no organizational involvement, and grants from the Medical Research Council, National Institute of Heath Research, Westminster Children's Trust Fund, Child Growth Foundation, Action Medical Research, HCA International, Danone, Bliss, British Heart Foundation, and the Department of Health. ELT, SJ, GD, KML, JRCP, SU, SS, and JDB declared no conflicts of interest.

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Erratum

Mason C, Xiao L, Imayama I, Duggan C, Wang C-Y, Korde L, McTiernan A. Vitamin D_3 supplementation during weight loss: a double-blind randomized controlled trial. Am J Clin Nutr 2014;99:1015–25.

The units for C-reactive protein (CRP) are incorrectly stated as ‘‘mg/mL’’ in the following places: the Results section of the Abstract on page 1015, the Results section of the text on page 1020, Table 2 on page 1020, Table 3 on page 1021, and Table 4 on page 1022. The correct unit is ‘‘mg/L.’’

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Erratum

Gale C, Thomas EL, Jeffries S, Durighel G, Logan KM, Parkinson JRC, Uthaya S, Santhakumaran S, Bell JD, Modi N. Adiposity and hepatic lipid in healthy full-term, breastfed, and formula-fed human infants: a prospective short-term longitudinal cohort study. Am J Clin Nutr 2014;99:1034–40.

Because of a copyediting error, the abbreviation for magnetic resonance spectroscopy (MRS) incorrectly appears in the fourth paragraph of the Subjects and Methods section. The first sentence of the fourth paragraph [‘‘Whole-body MRS images were acquired on a Phillips 1.5 Tesla system by using a T_1-weighted rapid-spin-echo sequence (repetition time of 500 ms, echo time of 17 ms, echo train length of 3) by using a Q body coil.’’] should read as follows: ‘‘Whole body magnetic resonance images were acquired on a Phillips 1.5 Tesla system by using a T_1-weighted rapid-spin-echo sequence (repetition time of 500 ms, echo time of 17 ms, echo train length of 3) by using a Q body coil.’’ The fifth sentence of the fourth paragraph [‘‘All MRS images were analyzed independently of the investigators and blind to participant identity and feeding group by VardisGroup (www.vardisgroup.com) by using an image segmentation program (SliceOmatic; Tomovision).’’] should read as follows: ‘‘All magnetic resonance images were analyzed independently of the investigators and blind to participant identity and feeding group by VardisGroup (www.vardisgroup.com) by using an image segmentation program (SliceOmatic; Tomovision).’’

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