Growth of infants consuming whey-predominant term infant formulas with a protein content of 1.8 g/100 kcal: a multicenter pooled analysis of individual participant data[1,2]

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ABSTRACT

Background: High protein intake during infancy may contribute to obesity later in life in infants who are not exclusively breastfed. Lowering the protein content of infant formula so it is closer to that of mature breast milk may reduce long-term risk of overweight or obesity in formula-fed infants.

Objective: We assessed the effects of whey-predominant formulas with a protein content of 1.8 g/100 kcal (lower than that in most current formulas and closer to breast milk) on infant growth by comparing against WHO growth standards and breastfed infants.

Design: A multicenter pooled analysis was conducted with the use of individual participant data (n = 1882) from 11 randomized controlled trials of healthy term infants. Mixed-effects models that used ANCOVA were generated to estimate weight-for-age z score (WAZ), as well as length-for-age, BMI-for-age, and head circumference–for-age z scores at age 4 mo in infants fed a lower-protein infant formula (LPF) or a lower-protein infant formula with additional active ingredients (probiotics, prebiotics, or both) (LPFA) and breastfed infants. Estimates, including 95% CIs, were compared with a ±0.5 SD of WHO growth standards, a benchmark for clinically significant differences.

Results: The 95% CIs for pooled estimates of WAZ were within ±0.5 SD of WHO growth standards for the LPF [0.07 (−0.16, 0.29)] and LPFA [0.22 (0.01, 0.43)] groups. WAZ was higher in the LPF ($P < 0.001$) and LPFA ($P = 0.003$) groups than in the breastfed infants, likely because breastfed infants had a relatively low WAZ [−0.23 (−0.51, 0.05)] compared with WHO growth standards. The 95% CIs for all other z scores in the LPF and LPFA groups were within ±0.5 SD of WHO growth standards, except for head circumference, for which the upper limit of the 95% CI slightly exceeded 0.5 SD. No difference was observed in any z scores between the LPF and LPFA groups.

Conclusion: Whey-predominant infant formula with a lower protein content that more closely resembles that of breast milk supports healthy growth comparable to the WHO growth standards and close to breastfed infants. *Am J Clin Nutr* 2016;104:1083–92.

Keywords: multicenter, individual participant data, pooled analysis, low-protein infant formula, breast milk, infant growth, probiotics, prebiotics

INTRODUCTION

Accumulating scientific evidence has shown that the kinetics of early growth, such as rapid weight gain after birth, may be associated with later risk of obesity and possible chronic disease outcomes (1–4). Breastfeeding, compared with feeding traditional (high-protein) formulas, has been identified as a protective factor against obesity later in life (5–8). Although the underlying biological mechanisms are not entirely clear, one theory, known as the "early protein hypothesis," attributes this possible protective relation to the protein content of feedings (5, 6). Specifically, formula-fed infants may be exposed to a high amount of protein that may increase their risk of later undesirable health outcomes. Therefore, a better understanding of the potential relation between lower protein intake in early infancy and growth may have important implications for obesity prevention.

Because of the difference in protein quality between breast milk and infant formula, a higher protein content in many infant formulas traditionally has been required to ensure that infants receive adequate amounts of amino acids for growth and development (9). However, advances in protein technology have led to the development of a higher-quality whey-predominant protein (10) that is used to manufacture lower-protein infant formula (LPF)[10] and

[1] Funded by Nestlé Nutrition, Vevey, Switzerland. Nestec provided study products and funding support for all 11 studies included in the analysis. This is a free access article, distributed under terms (http://www.nutrition.org/publications/guidelinesand-policies/license/) that permit unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

[2] Supplemental Figures 1 and 2 and Supplemental Table 1 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[10] Abbreviations used: BMIAZ, BMI-for-age z score; HCAZ, head circumference–for-age z score; IPD, individual participant data; LAZ, length-for-age z score; LPF, lower-protein infant formula; LPFA, lower-protein infant formula with additional active ingredients (probiotics, prebiotics, or both); RCT, randomized controlled trial; WAZ, weight-for-age z score.

Received January 19, 2016. Accepted for publication July 28, 2016.
First published online September 7, 2016; doi: 10.3945/ajcn.116.130633.

lower-protein infant formula with additional active ingredients (probiotics, prebiotics, or both) (LPFA). At 1.8 g protein/100 kcal, the protein-to-energy ratio of LPF and LPFA is closer to that of breast milk and represents the lowest regulatory permissible limit for protein in infant formula in the United States and the European Union (11–13).

The protein concentration of LPF and LPFA has been demonstrated to be safe while supporting early growth patterns and metabolic outcomes closer to those of breastfed infants (14). Although individual randomized controlled trials (RCTs) have demonstrated that LPFs and LPFAs support adequate infant growth, to our knowledge, anthropometric outcomes from these randomized trials have not been synthesized with the use of systematic methodology. Furthermore, as noted in the comments on infant formula supplemented with probiotics and/or prebiotics in 2010 by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (15), better understanding of the health effects of such formulas compared with formula without probiotics or prebiotics is warranted. Although preliminary pooled analyses of weight-for-age *z* score (WAZ) from some studies have been reported in 2 recent reviews (16, 17), to our knowledge, no study to date has systematically pooled all of the individual-level growth data from different trials for infants receiving LPF, including those containing active ingredients, and compared them against the WHO growth standards and with breastfed infants. Pooled analysis of individual data across multiple trials can enhance the statistical precision to estimate growth parameters in infants fed LPF or LPFA while accounting for geographic and cultural variability.

Therefore, we conducted a pooled analysis with the use of individual participant data (IPD) across 11 randomized trials of LPF and LPFA. In a traditional meta-analysis, summary statistics are combined across studies, which may be subject to design variation, use of differing analytic metrics, and variable definitions of exposures and outcomes. Our approach allowed us to perform a pooled analysis of IPD across 11 primary RCTs, thus making it possible to create unified variable definitions and adjust for influencing covariates such as birth characteristics (18). Specifically, we *1*) evaluated the growth of infants fed LPF or LPFA and breastfed infants by comparing the anthropometric *z* scores against the 2006 WHO growth standards (19), with WAZ as the primary endpoint, and *2*) compared anthropometric *z* scores in LPF-fed, LPFA-fed, and breastfed infants.

METHODS

Study design and inclusion of individual studies

Currently, the most commonly used infant formula globally with 1.8 g protein/100 kcal is a whey-predominant infant formula (**Supplemental Table 1**) from Nestlé Nutrition. This formula has been tested in multiple clinical trials that have included infant growth as an outcome, thereby providing a rich source of data on infant formula with a specific and homogeneous protein content, in terms of both protein quantity and quality. We had access to the participant-level data for all included trials, which allowed the use of a more rigorous IPD pooled analysis design than would a traditional meta-analysis design based on summary statistics reported by the individual studies. Eligibility criteria for inclusion of trials in the pooled analysis included the following: *1*) double-blind, randomized controlled design; *2*) evaluation of healthy term infants; *3*) infants in ≥1 study arm fed whey-predominant infant formula with a protein content of 1.8 g/100 kcal; *4*) results that included WAZ, length-for-age *z* score (LAZ), BMI-for-age *z* score (BMIAZ), and head circumference–for-age *z* score (HCAZ); and *5*) infants either exclusively formula-fed from ≤4 wk of age to ≥4 mo of age (formula-fed arms) or exclusively breastfed from birth to ≥4 mo of age (breastfed arms). All included trials had parallel infant formula group designs, with some having a nonrandomized breastfed reference group as well. Research staff and infants' parents were blinded to the type of formula during study follow-up. All trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practices and were approved by respective institutional ethics committees.

Comparison with 2006 WHO Child Growth Standards

In the current analysis, *z* scores were calculated to compare infants' growth with the 2006 WHO standards. *Z* scores represent the number of SD units above or below the median of the WHO standard curves for healthy child growth, which were developed based on the WHO Multicenter Growth Reference Study (19). The WHO growth standards have been widely accepted as the standard on how infants and young children should grow (20).

Data synthesis and statistical analyses

We pooled individual-level data across trials while following a modified version of the Preferred Reporting Items for a Systematic Review and Meta-Analysis of Individual Participant Data guidelines to ensure the validity and accurate reporting of data (21).

IPD from all trials were merged into a single database. To be included in the pooled analysis, a subject needed to have data at birth and month 4 and also have data for the 2 additional covariates included in the statistical model, infant sex and delivery type. This allowed us to take advantage of the pooling structure of the analysis by harmonizing covariates across different centers. All data were carefully reviewed for missing values or data entry errors according to standard quality control procedures. This was done for both baseline information and outcome measurements. Among the few database errors identified were negative ages, no birth weight data, and inconsistent head circumference data. These accounted for <10 infants throughout all study centers, and data for these participants were omitted from the analyses. The data management flow diagram is presented in **Supplemental Figure 1**. Baseline categorical data were analyzed with the use of a chi-square test, and baseline continuous data were analyzed with the use of ANOVA. Overall comparison of the 3 groups was conducted first, and if this was significant at $P \leq 0.05$, pairwise comparisons were done.

The primary objective was to assess the growth of LPF-fed, LPFA-fed, and breastfed infants by comparing anthropometric *z* scores with WHO growth standards. The primary endpoint was WAZ at 4 mo of age. Four months was selected as a clinically relevant time point that would avoid significant confounding from the introduction of complementary feeding between 4 and 6 mo of age. To achieve the primary objective, WAZ, LAZ, BMIAZ, and HCAZ were calculated with the use of publicly available macros from the WHO website. The *z* score estimates at 4 mo from the individual studies were derived by ANCOVA while adjusting for corresponding birth *z* scores, infant sex, and

type of delivery. A 2-step procedure that used mixed-effects (fixed and random) models was used for all primary analyses (18). I^2 was calculated for the primary endpoint (WAZ) as an indicator of the proportion of heterogeneity in the meta-analysis model. In the first step, fixed-effects models with the use of IPD were generated with ANCOVA that corrected for corresponding birth *z* scores, infant sex, delivery type, and study. In the second step, random-effects models were created to estimate the overall weighted group mean effects while accounting for between-study variance, with the use of the study-specific group mean estimates and variance data. This allowed us to use and control for the individual data in all infants, estimate the within-group variance for each study, and produce overall summary effects while accounting for both within- and between-study variability. Finally, the *z* score estimates and 95% CIs were compared with ±0.5 SD of the WHO growth standards. Specifically, when the lower bound of the 95% CI was >−0.5 SD and the higher bound of the 95% CI was <0.5 SD, anthropometric parameters were considered to be not statistically or clinically different from the WHO growth standards. The selection of ±0.5 SD as the clinically significant benchmark for WAZ is consistent with previous studies (20, 22, 23) and with the recommendation from the American Academy of Pediatrics to use 3 g/d as a clinically relevant difference in weight gain in infant feeding clinical trials (24). A growth difference of 3 g/d will result in a 366 g difference in weight gain after 4 mo. When compared against the WHO growth standard at 4 mo, 366 g translates to a 0.52 SD for girls and a 0.50 SD for boys. Thus, as a measure of clinical relevance, a 3-g/d difference in weight gain translates into a ±0.5 SD for WAZ at 4 mo. The same benchmark of ±0.5 SD was also used as an indication of clinical significance for other anthropometric parameters in the study, and this is consistent with previous studies that applied 0.5 SD as a benchmark for assessing infant LAZ and HCAZ (20, 22, 23).

The secondary objective of our analysis was to compare the growth of infants fed LPF or LPFA with that of breastfed infants. To achieve this objective, *z* scores were compared between the 3 feeding groups with the use of ANCOVA with feeding group as the factor in the model while adjusting for corresponding birth *z* scores, infant sex, delivery type, and study. As an exploratory analysis, we evaluated the rate of weight gain based on change in WAZ from birth to 4 mo of age (WAZ at 4 mo minus WAZ at birth) between the 3 feeding groups. The change in WAZ was classified as "slow" (<−0.67), "gradual" (−0.67 to 0.67), or "rapid" (>0.67). Such classification based on increments of 0.67 SD has been used in previous studies (25, 26), and the 3 categories for change in WAZ are equivalent to downward, average, and upward crossings of major weight percentiles, with a 0.67 SD change corresponding to a change in one major percentile band (e.g., 50th to 75th) on a growth chart (25). Rapid early weight gain (change of >0.67) has been linked to an increased risk of overweight in later life (25). The distribution of infants in these 3 categories was compared between the LPF, LPFA, and breastfed groups with the use of a chi-square test. A Fisher's exact test subsequently was used for pairwise comparisons. In previous studies (25, 26), the classification was applied to the change in WAZ from birth to age 6 mo. However, to avoid potential confounding effects of complementary feeding on the rate of weight gain, we focused on the change from birth to 4 mo, when infants still were fed exclusively with either formula or breast milk.

All statistical analyses were conducted with the use of SAS Statistical Software, version 9.1. Data reported are estimated means (95% CIs) unless otherwise noted.

RESULTS

Characteristics of infants included in the pooled analysis

Individual-level data from 11 RCTs were included in the multicenter pooled analysis (**Table 1**). Studies were conducted between 1998 and 2008 and were performed in 6 different countries on 4 different continents. Ten studies used LPF as an infant feeding arm; 9 studies used LPFA that contained prebiotics, probiotics, or both; and 5 studies used breastfed infants as a reference arm. The overall dropout rate among all study participants was ∼24%, with slightly higher rates of dropout in the breastfed groups than in the formula-fed groups (30% compared with 22%). We pooled data from a total of 1882 healthy term infants; 737 in the LPF group, 965 in the LPFA group, and 180 in the breastfed group met all predefined requirements for the WAZ endpoint analysis. The number of infants included in the other growth endpoint analyses was somewhat lower because of missing baseline values (**Table 2**). The proportion of male and female infants was balanced (∼1:1) in each of the 3 feeding groups. There was a significantly higher rate of cesarean section delivery in the LPF and LPFA groups than in the breastfed group, and the 2 groups of formula-fed infants had significantly lower WAZ and BMIAZ at birth than did the breastfed group (Table 2).

WAZ at 4 mo of age

The pooled WAZ estimate for the LPF group was 0.07 (−0.16, 0.29) based on analysis of 737 infants from 10 studies (**Figure 1**). The 95% CI range for the pooled estimate was well within ±0.5 SD of the WHO growth standards; this was also true for 7 of the 10 studies with LPF arms. Results from individual studies were relatively homogeneous, with the exception of the study conducted in China (31), in which the mean estimate for WAZ was 0.92 and the lower bound of the 95% CI was 0.79 (which is >0.5 SD). A sensitivity analysis conducted without the data from this study resulted in a pooled WAZ estimate of −0.03 (−0.12, 0.05) based on analysis of 554 infants. Furthermore, the I^2 heterogeneity test was 94% with the China study included, but the model became homogeneous after removal of this study (I^2 = 8%).

The pooled WAZ estimate for the LPFA group was 0.22 (0.01, 0.43) based on analysis of 965 infants from 9 studies (Figure 1). Similar to the LPF analysis results, the 95% CI for the pooled estimate was within ±0.5 SD; this was also true for 6 of 9 studies with LPFA arms. The China study (31) again appeared to be an outlier, with a mean WAZ estimate of 0.81 and a lower bound of the 95% CI of 0.68. When this study was removed in a sensitivity analysis (n = 776), the pooled WAZ estimate was 0.14 (0.02, 0.26) and the proportion of variance due to heterogeneity (I^2) changed from 92% to 42%.

The pooled WAZ estimate for the breastfed group was −0.23 (−0.51, 0.05) based on analysis of 180 infants from 5 studies (Figure 1), with an I^2 of 64%. The pooled mean WAZ estimate was skewed slightly lower than the WHO growth standards by data from 2 French studies (32, 33), both of which had mean WAZ estimates and corresponding lower bounds of the 95% CIs that were <−0.5 SD.

TABLE 1
Studies included in the multicenter IPD pooled analysis[1]

Study, year	Study arms included in the pooled analysis	Reference
Italy, 1998	Formula-fed: 1.8 g protein/100 kcal	Räihä et al., 2002 (14)
	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs	
	Breastfed	
Italy, 1999	Formula-fed: 1.8 g protein/100 kcal	Barclay et al., 2003 (27)
	Formula-fed: 1.8 g protein/100 kcal + prebiotics (Raftilose)	
	Formula-fed: 1.8 g protein/100 kcal + probiotics (BB12)	
	Formula-fed: 1.8 g protein/100 kcal + prebiotics (Raftilose) + probiotics (BB12)	
Australia, 2002	Formula-fed: 1.8 g protein/100 kcal	Gibson et al., 2009 (28)
	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs + probiotics (*B. lactis* CNCM I-3446)	
Italy, 2003	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs	Puccio et al., 2007 (29)
	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs + prebiotics (BMOSs) + probiotics (BL999)	
France, 2003	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs	Chouraqui et al., 2008 (30)
	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs + probiotics (BL999 + LPR)	
	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs + prebiotics (BMOSs) + probiotics (BL999 + LPR)	
	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs + prebiotics (BMOSs) + probiotics (BL999 + ST11)	
China, 2003	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs	Wu et al., 2016 (31)
	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs + probiotics (BL999)	
France, 2005a	Formula-fed: 1.8 g protein/100 kcal	Putet et al., 2016 (32)
	Breastfed	
France, 2005b	Formula-fed: 1.8 g protein/100 kcal	Hascoët et al., 2011 (33)
	Formula-fed: 1.8 g protein/100 kcal + probiotics (BL999)	
	Breastfed	
Italy, 2005	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs	Meli et al., 2014 (34)
	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs + prebiotics (BMOSs)	
	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs + prebiotics + probiotics (BMOSs + BL999 + LPR)	
	Breastfed	
South Africa, 2007	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs	Cooper et al., 2015 (35)
	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs + prebiotics (BMOSs) + probiotics (*B. lactis* CNCM I-3446)	
Greece, 2008	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs + probiotics (*B. lactis* CNCM I-3446)	Baglatzi et al., 2016 (36)
	Formula-fed: 1.8 g protein/100 kcal + LCPUFAs + probiotics (*B. lactis* CNCM I-3446, higher level)	
	Breastfed	

[1]BB12, *Bifidobacterium lactis* BB12; BL999, *Bifidobacterium longum* (ATCC BAA999); BMOS, bovine milk–derived oligosaccharides; IPD, individual participant data; LCPUFA, long-chain PUFA; LPR, *Lactobacillus rhamnosus* CGMCC 1.3724; ST11, *Lactobacillus paracasei* CNCM I-2116.

When compared between the 3 feeding groups (**Table 3**), the WAZ estimates were significantly higher in the LPF ($P < 0.001$) and LPFA ($P = 0.003$) groups than they were in the breastfed group. The mean WAZ differences were 0.30 (0.14, 0.46) for the LPF group compared with breastfed infants and 0.24 (0.08, 0.39) for the LPFA group compared with breastfed infants; both differences were <0.5 SD. No significant difference was detected between the LPF and LPFA groups on WAZ estimates ($P = 0.17$).

LAZ at 4 mo of age

The pooled LAZ estimates for the LPF, LPFA, and breastfed groups (**Figure 2**) were −0.02 (−0.20, 0.17), 0.14 (−0.06, 0.34) and 0.19 (0.04, 0.34) based on analysis of 699, 921, and 180 infants from 10, 9, and 5 studies, respectively. The 95% CIs of the pooled estimates were all within ±0.5 SD. No statistically significant differences in LAZ estimates were detected between the LPF, LPFA, and breastfed groups ($P > 0.16$, Table 3).

BMIAZ at 4 mo of age

The pooled BMIAZ estimates for the LPF and LPFA groups (**Figure 3**) were 0.07 (−0.19, 0.33) and 0.11 (−0.10, 0.33) based on analysis of 699 and 921 infants from 10 and 9 studies, respectively. The 95% CIs for both groups were within ±0.5 SD. Similar to with the WAZ results, the China study (31) appeared to be an outlier, with mean BMIAZ estimates of 0.89 and 0.69 with lower bounds of the 95% CIs of 0.70 and 0.52 (both of which were >0.5 SD).

The pooled BMIAZ estimate for the breastfed group (Figure 3) was −0.53 (−0.79, −0.28) based on analysis of 180 infants from 5 studies. Results from individual studies were homogeneous, with mean BMIAZ estimates for all individual studies close to or below −0.5 SD. When compared with the LPF and LPFA groups (Table 3), the breastfed group had significantly lower BMIAZ ($P < 0.001$ for breastfed infants compared with the LPF group and $P = 0.001$ for BF infants compared with the LPFA group). The difference was driven by the low BMIAZ for the breastfed group, with BMIAZ estimates for the LPF

TABLE 2
Baseline characteristics of infants included in the IPD pooled analysis according to feeding groups[1]

	LPF	LPFA	BF
Studies included, *n*	10	9	5
Female	50	49	49
Cesarean section delivery	43	52	27*
Birth WAZ (*n*)	−0.10 ± 0.84 (737)	−0.12 ± 0.90 (965)	0.14 ± 0.77 (180)[#]
Birth LAZ (*n*)	0.03 ± 1.07 (700)	0.09 ± 1.08 (921)	0.21 ± 0.91 (180)
Birth BMIAZ (*n*)	−0.17 ± 1.08 (700)	−0.27 ± 1.13 (921)	0.05 ± 0.99 (180)[#]
Birth HCAZ[2] (*n*)	0.14 ± 1.07 (554)	0.22 ± 1.06 (775)	0.30 ± 0.93 (180)

[1]Values are means ± SDs or percentages, unless otherwise indicated. Categorical data were analyzed with the use of a chi-square test, and continuous data were analyzed with the use of ANOVA. An overall comparison between 3 groups was conducted first, and if significant at $P \leq 0.05$, pairwise comparisons between 2 groups were obtained. *LPF and LPFA are significantly different from BF and are also different from each other at $P \leq 0.05$. [#]LPF and LPFA are significantly different from BF but not different from each other. BF, breastfed; BMIAZ, BMI-for-age *z* score; HCAZ, head circumference–for-age *z* score; IPD, individual participant data; LAZ, length-for-age *z* score; LPF, lower-protein infant formula; LPFA, lower-protein infant formula with additional active ingredients (probiotics, prebiotics, or both); WAZ, weight-for-age *z* score.
[2]Birth HCAZ of infants from the study conducted in China (31) (which included LPF and LPFA arms) was not available.

and LPFA groups being similar to the WHO growth standards (Figure 3).

HCAZ at 4 mo of age

The pooled HCAZ estimates for the LPF and LPFA groups (**Figure 4**) were 0.37 (0.19, 0.55) and 0.45 (0.28, 0.62) based on analysis of 736 and 959 infants from 10 and 9 studies, respectively. Results from individual studies of these 2 groups were homogeneous, with mean HCAZ estimates close to 0.5 SD, except for those for the South Africa study (35), in which mothers of infants were HIV-positive. Interestingly, infants fed LPF and LPFA in the South Africa study exhibited mean HCAZ estimates close to 1 SD. The pooled HCAZ estimate for the breastfed group (Figure 4) was 0.27 (0.13, 0.4) based on analysis of 178 infants from 5 studies. No significant differences between the LPF, LPFA, and breastfed groups were detected on HCAZ estimates ($P > 0.4$, Table 3).

Rate of weight gain based on change in WAZ from birth to age 4 mo

The proportion of infants in weight gain categories based on change in WAZ differed ($P < 0.001$) between the LPF, LPFA, and breastfed groups (**Figure 5**A). Specifically, compared with

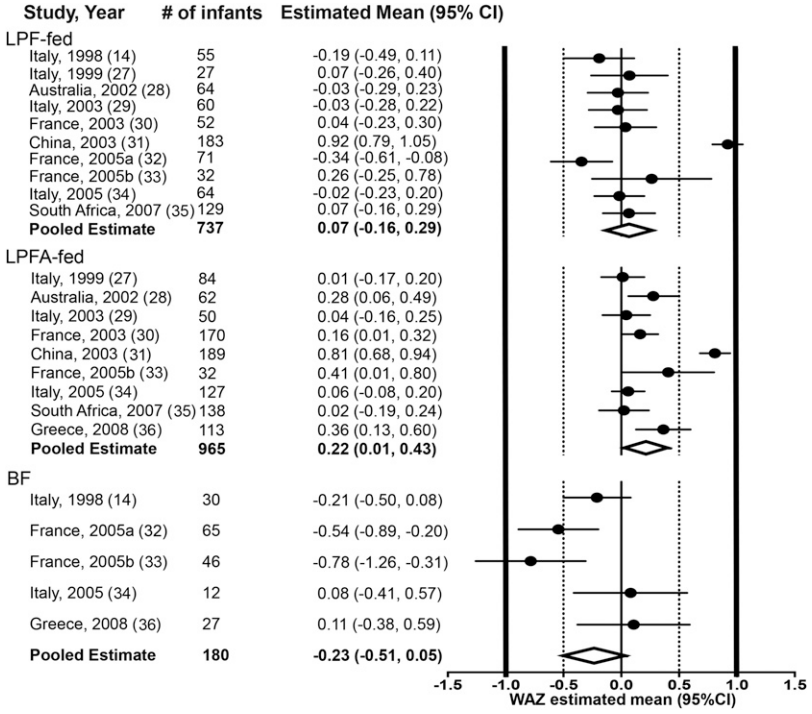

FIGURE 1 IPD pooled analysis of WAZ in infants at 4 mo of age for the LPF, LPFA, and BF groups. Values are estimated means calculated from ANCOVA with the use of random-effects models adjusted for birth WAZ, infant sex, delivery type, and study. The solid circles represent the estimated mean from individual studies, and the horizontal lines represent the 95% CIs for the mean. The diamonds represent the pooled mean estimate, with the horizontal tips of the diamond representing the lower and upper limits of the 95% CIs. BF, breastfed; IPD, individual participant data; LPF, lower-protein infant formula; LPFA, lower-protein infant formula with additional active ingredients (probiotics, prebiotics, or both); WAZ, weight-for-age *z* score.

TABLE 3
Anthropometric *z* score differences between feeding groups at age 4 mo[1]

	LPF vs. BF	LPFA vs. BF	LPFA vs. LPF
WAZ difference	0.30 (0.14, 0.46)*	0.24 (0.08, 0.39)*	−0.06 (−0.15, 0.03)
LAZ difference	0.04 (−0.15, 0.23)	−0.03 (−0.21, 0.15)	−0.07 (−0.17, 0.03)
BMIAZ difference	0.37 (−0.19, 0.33)*	0.11 (−0.10, 0.33)*	−0.53 (−0.79, −0.28)
HCAZ difference	0.02 (−0.16, 0.19)	−0.01 (−0.18, 0.15)	−0.03 (−0.12, 0.06)

[1]Values are estimated *z* score mean differences (95% CIs) between feeding groups (LPF − BF, LPFA − BF, and LPFA − LPF) calculated from ANCOVA while adjusting for corresponding birth *z* scores, infant sex, delivery type, and study. *$P \leq 0.003$. BF, breastfed; BMIAZ, BMI-for-age *z* score; HCAZ, head circumference–for-age *z* score; LAZ, length-for-age *z* score; LPF, lower-protein infant formula; LPFA, lower-protein infant formula with additional active ingredients (probiotics, prebiotics, or both); WAZ, weight-for-age *z* score.

the breastfed group, the LPF ($P < 0.001$) and LPFA ($P < 0.001$) groups had a lower proportion of infants in the slow category (22% and 18%, respectively, compared with 42%), a similar proportion of infants in the gradual category (48% and 50%, respectively, compared with 49%) and a higher proportion of infants in the rapid category (30% and 32%, respectively, compared with 9%). No difference was detected between the LPF and LPFA groups ($P = 0.13$).

The China study (31) again appeared to be an outlier (**Supplemental Figure 2**), with 57% and 54% of infants in the rapid category for the LPF and LPFA groups, respectively. In addition, the China study did not include a breastfed reference group; therefore, no Chinese infants were included in the breastfed group in the current analysis. Further analysis that excluded data from the China study showed that the proportions of infants in weight gain categories in the LPF ($P < 0.001$) and LPFA ($P < 0.001$) groups still differed from those of the breastfed group, but were numerically closer (Figure 5B), i.e., 21% and 26% instead of 30% and 32% in the rapid category for the LPF and LPFA groups, respectively. After the China study was excluded, the LPF group differed from the LPFA group ($P = 0.015$), with a higher proportion of infants in the slow category (27% compared with 22%), no difference in the gradual category (52% compared with 52%), and a lower proportion in the rapid category (21% compared with 26%).

DISCUSSION

We conducted a comprehensive pooled analysis on individual data from 1882 healthy term infants in 11 RCTs to evaluate the effects of a whey-predominant infant formula with lower protein content with and without added active ingredients (prebiotics, probiotics, or both) on growth parameters at 4 mo of age. Using

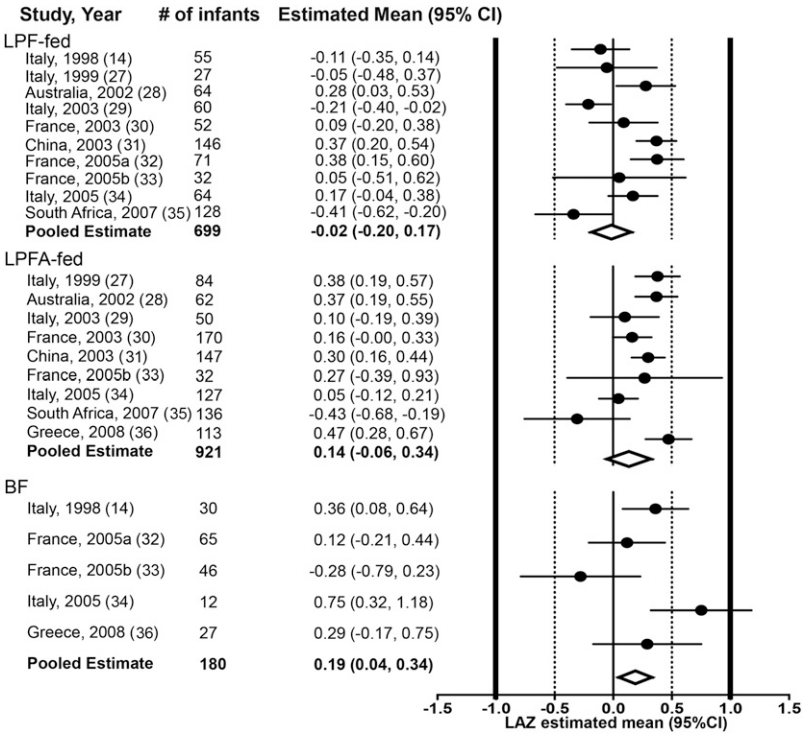

FIGURE 2 IPD pooled analysis of LAZ in infants at 4 mo of age for the LPF, LPFA, and BF groups. Values are estimated means calculated from ANCOVA with the use of random-effects models adjusted for birth LAZ, infant sex, delivery type, and study. The solid circles represent the estimated mean from individual studies, and the horizontal lines represent the 95% CIs for the mean. The diamonds represent the pooled mean estimate, with the horizontal tips of the diamond representing the lower and upper limits of the 95% CIs. BF, breastfed; IPD, individual participant data; LAZ, length-for-age *z* score; LPF, lower-protein infant formula; LPFA, lower-protein infant formula with additional active ingredients (probiotics, prebiotics, or both).

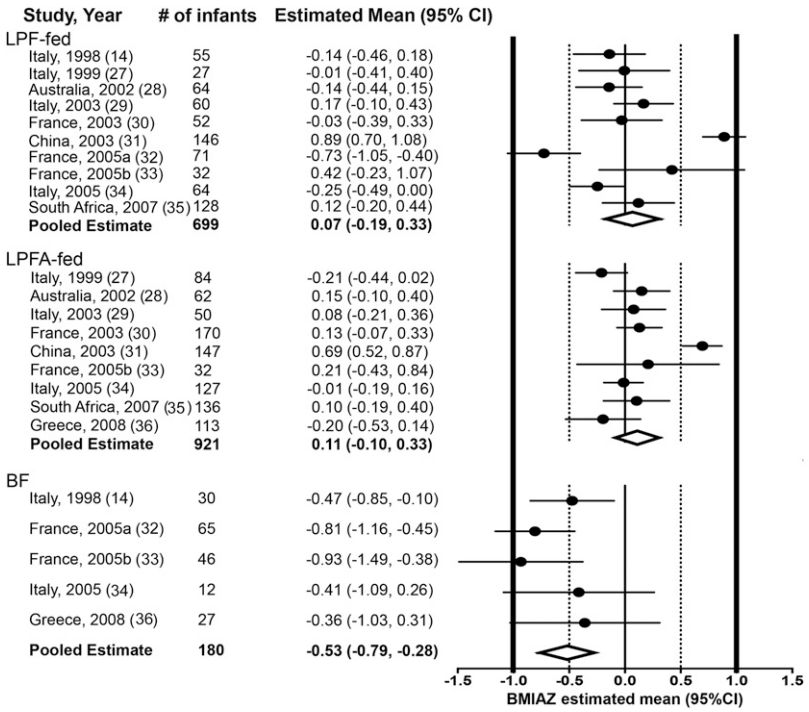

FIGURE 3 IPD pooled analysis of BMIAZ in infants at 4 mo of age for the LPF, LPFA, and BF groups. Values are estimated means calculated from ANCOVA with the use of random-effects models adjusted for birth BMIAZ, infant sex, delivery type, and study. The solid circles represent the estimated mean from individual studies, and the horizontal lines represent the 95% CIs for the mean. The diamonds represent the pooled mean estimate, with the horizontal tips of the diamond representing the lower and upper limits of the 95% CIs. BF, breastfed; BMIAZ, BMI-for-age *z* score; IPD, individual participant data; LPF, lower-protein infant formula; LPFA, lower-protein infant formula with additional active ingredients (probiotics, prebiotics, or both).

pooled analysis methodology of IPD, we were able to further analyze study data by harmonizing the covariates under study with uniform analytic metrics (e.g., correcting for baseline characteristics). Our pooled analyses generated summary associations with greater precision (i.e., enhanced statistical power) than any of the individual studies. By virtue of combining individual data, we created a single, larger analysis with greater analytic control. This methodology is widely used (e.g., in the Harvard Pooling Project of Prospective Studies of Diet and Cancer; https://www.hsph.harvard.edu/pooling-project/about-the-study/).

The results of our analyses showed that a whey-predominant infant formula with a protein content of 1.8 g/100 kcal supports healthy growth that is comparable to the WHO growth standards. Specifically, the WAZ, LAZ, and BMIAZ pooled estimates and 95% CIs at 4 mo in LPF- or LPFA-fed infants were well within ±0.5 SD of the WHO growth standards. However, there was some degree of data inflection within some of the models. This mainly was due to outlier results from one study conducted in Shanghai, a major urbanized city in China. The estimates for WAZ and BMIAZ at 4 mo of age for LPF- and LPFA-fed infants from the Chinese study (31) were considerably higher than those from the other studies included in the analysis. This observation is consistent with a recent publication (37) based on the Chinese fourth National Survey on the Physical Growth and Development of Children, which reported that urban Chinese infants were heavier than those included in the WHO Multicenter Growth Reference Study. Regardless, the exclusion of data from this Chinese study did not modify the pooled results significantly. The results of our analyses also showed that including specific active ingredients (i.e., prebiotics, probiotics, or both) in LPF did not significantly affect growth parameters at 4 mo of age. This is consistent with a recent systematic review by Szajewska et al. (38), which showed that infants fed *Bifidobacterium lactis*–supplemented formula grew at a rate that was similar to that of infants fed unsupplemented formula. One major difference between our analysis of formula supplemented with active ingredients and that of Szajewska et al. (38) is that our LPFA group included several different types of active ingredients: different strains of probiotics (e.g., *B. lactis* CNCM I-3446, BL999) or prebiotics (bovine milk–derived oligosaccharides), or both. An interesting finding is that the change in WAZ from birth to 4 mo of age differed between the LPF and LPFA groups (Figure 5) after the China study was excluded; however, interpretation of this finding should be made in the context of the exploratory and descriptive nature of this particular analysis.

It is noteworthy that HCAZ estimates of LPF- and LPFA-fed infants were consistently higher than the WHO growth standards, with infants in the South Africa study of HIV-positive mothers exhibiting the greatest deviation. HCAZ estimates in breastfed infants included in the analysis were also similarly higher than the WHO standard. These HCAZ results mirrored the findings from a recent systematic review (20), which showed that the WHO head circumference data are at the lower end of head circumference measurements from large studies of economically advantaged children in 30 countries. The observed difference between the WHO head circumference standard and recent studies (including ours) may be the result of differences in head circumference measurement techniques; however, as noted in Natale et al. (20), there is still a sizable difference between the WHO head circumference data and a large European study that used a strict

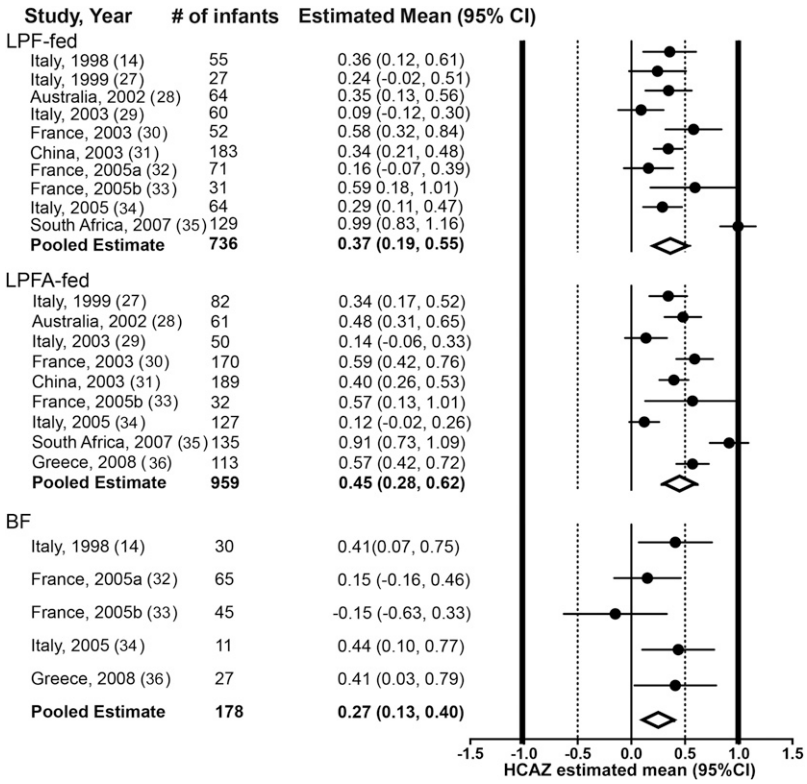

FIGURE 4 IPD pooled analysis of HCAZ in infants at 4 mo of age for the LPF, LPFA, and BF groups. Values are estimated means calculated from ANCOVA with the use of random-effects models adjusted for birth HCAZ (birth HCAZ for the China study (31) was not available, and birth WAZ was used instead for this study), infant sex, delivery type, and study. The solid circles represent the estimated mean from individual studies, and the horizontal lines represent the 95% CIs for the mean. The diamonds represent the pooled mean estimate, with the horizontal tips of the diamond representing the lower and upper limits of the 95% CIs. BF, breastfed; HCAZ, head circumference–for-age *z* score; IPD, individual participant data; LPF, lower-protein infant formula; LPFA, lower-protein infant formula with additional active ingredients (probiotics, prebiotics, or both); WAZ, weight-for-age *z* score.

standardized measurement technique that mirrored the WHO study methodology (39). Collectively, our IPD pooled analysis findings support the conclusion of Natale et al. (20), and suggest that additional research may be needed to justify using a single international head circumference standard.

An interesting finding from our IPD pooled analysis was that breastfed infants appeared to deviate from the WHO growth standards for weight, length, and BMI to a larger extent than did LPF- or LPFA-fed infants. Specifically, breastfed infants in our study tended to be lighter and longer, and therefore manifested

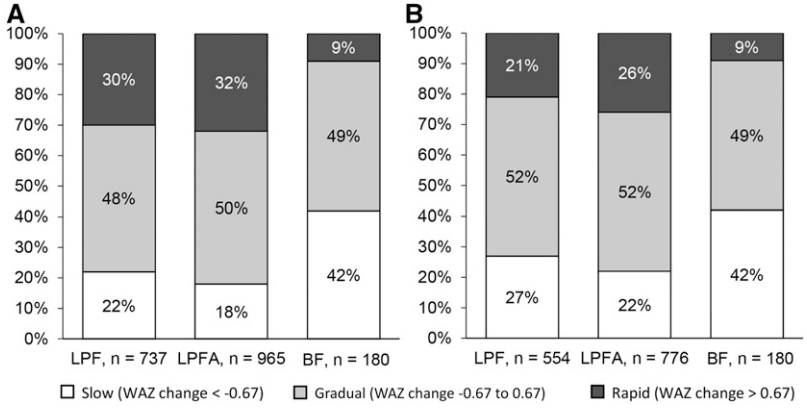

FIGURE 5 Rate of weight gain between birth and 4 mo of age for the LPF, LPFA, and BF groups. IPD from all studies (A). The LPF ($P < 0.001$) and LPFA ($P < 0.001$) groups were significantly different from the BF group, whereas no difference between the LPF and LPFA groups was detected ($P = 0.13$). IPD from all studies excluding the China study (31) (B). The LPF ($P < 0.001$) and LPFA ($P < 0.001$) groups were significantly different from the BF group, and the LPF group also was significantly different ($P = 0.015$) from the LPFA group. The WAZ change was calculated as WAZ at 4 mo of age minus WAZ at birth. Values are percentage of infants in weight-gain categories based on WAZ change as slow (<-0.67), gradual (-0.67 to 0.67), or rapid (>0.67). A chi-square test was used to compare the LPF, LPFA, and BF groups, and a Fisher's exact test subsequently was used for pairwise comparisons. BF, breastfed; IPD, individual participant data; LPF, lower-protein infant formula; LPFA, lower-protein infant formula with additional active ingredients (probiotics, prebiotics, or both); WAZ, weight-for-age *z* score.

a significantly lower BMI than the WHO growth standards. Multiple reasons may underlie this finding. For example, the breastfed infants in our analysis were from France, Italy, and Greece, all of which are countries not included in the WHO study. In addition, the sample size (n = 180) of the breastfed group was relatively small. Nonetheless, the relatively lower weight and BMI of the breastfed infants included in our analysis was acceptable, as it was within −2 SD of the WHO standards. The considerably homogeneous results of low BMIAZ in breastfed infants in the 5 European studies included in our analysis also are in agreement with the BMI z scores of the breastfed group in the European Childhood Obesity Trial (6), which included ∼500 breastfed infants from 5 European countries (Germany, Belgium, Italy, Poland, and Spain). Furthermore, the breastfed group from the Euro-Growth study also manifested relatively low WAZ (compared to WHO Growth Standards) at 4 mo of age (40). Additional research is warranted to explore any potential long-term implications of the relatively lower weight and BMI in early infancy in European infants.

Because early rapid weight gain has been shown to be associated with obesity risk in later life (25, 26, 41, 42), the rate of weight gain based on the change in WAZ was explored. In the LPF, LPFA, and breastfed groups, ∼50% of the infants were in the gradual weight-gain category. However, a relatively greater proportion of breastfed infants (42% compared with ≤27% of formula-fed infants) were in the slow category, and a relatively greater proportion of formula-fed infants (≥21% compared with 9% of breastfed infants) were in the rapid category, despite consumption of formulas with a lower protein content closer to that of breast milk. The observed difference in the rate of weight gain may arise in part from a higher milk intake in formula-fed infants than in breastfed infants (43). It also may be a statistical caveat, because there were fewer infants in the breastfed group (5 studies; n = 180). In addition, our ability to interpret these findings is somewhat restricted because it is uncertain whether the rate of weight gain in the breastfed group was skewed or truly reflective of how infants should grow. For example, it is theoretically desirable to have all infants in the gradual weight gain category; however, only ∼50% of the breastfed infants in the current analysis were in the gradual category, whereas 42% were in the slow category.

One of the major strengths of our analysis was the ability to pool individual-level data across 11 RCTs, with greater analytic control being facilitated by the ability to harmonize covariates, definitions, and analytic metrics. Another key strength was the randomized controlled design of the included studies. This type of design allows for greater control of influential confounding factors, and is less susceptible to residual confounding than observational studies. Moreover, there is control over the allocation and, in theory, the compliance with the type of infant feeding, given the experimental components of RCTs. Finally, the analysis of data over a decade of research, at different study centers, and across numerous geographic regions may have enhanced the generalizability of our research findings.

Some limitations of our analysis also warrant mention. We focused on infant formula with a lower-protein content (1.8 g protein/100 kcal) and a specific protein quality (whey-predominant); thus, findings may not be applicable to LPFs with a different protein quality (e.g., casein-predominant). Maternal height and BMI (important factors influencing child growth, which were not controlled in the analysis) may differ between the infant population evaluated in the WHO growth reference study and the studies included in this analysis. In addition, the RCTs used in the current analysis differed somewhat in terms of operational methodology; not all trials included both LPF and LPFA arms, and fewer trials included arms with breastfed infants, thus resulting in a variable proportion of infants representing the 3 study groups. However, given the fact that we were able to conduct the analysis on individual-level data, we had analytic latitude such that we could synchronize similar exposure groups and outcome classifications.

In conclusion, it is well established that obesity is a major public health burden in most developed countries, with a foretelling of risk in developing countries worldwide. Accumulating scientific evidence suggests that excessive protein intake during infancy may increase the subsequent risk of obesity. The results of our pooled analysis of IPD from 11 RCTs have indicated that feeding with a whey-predominant formula with a lower protein content (1.8 g/100 kcal, lower than most currently available infant formulas) that is closer to that of human milk, with or without pre- or probiotics, supports healthy early growth comparable to the WHO growth standards and close to that of breastfed infants. The different rate of weight gain based on the change in WAZ between breastfed infants and those fed LPF or LPFA warrants further investigation.

We thank the lead investigators of the 11 studies: Niels Räihä (Italy, 1998; Italy, 1999), Maria Makrides (Australia, 2002), Giuseppe Puccio (Italy, 2003; Italy, 2005), Jean-Pierre Chouraqui (France, 2003), Weiping Wang (China, 2003), Guy Putet and Jean-Charles Picaud (France, 2005a), Jean-Michel Hascoët (France, 2005b), Peter A Cooper (South Africa, 2007), and Christos Costalos (Greece, 2008).

The authors' responsibilities were as follows—JY, RSN, DG, PS, PE, ES-K, and FH: conceptualized and designed the study; RSN and DG: conducted the analysis; DDA, JY, and LCB: wrote the paper with input from all authors; and all authors: read and approved the final manuscript. DDA and LCB are employees of EpidStat Institute; JY, RSN, DG, PS, PE, and ES-K are employees of Nestlé; and FH was the chairman of the Nestlé Nutrition Institute at the time of initiation of the study.

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