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Early Weight Gain Forecasts Accelerated Eruption of Deciduous Teeth and Later Overweight Status during the First Year

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Abstract

Objectives.—To determine whether early diet and weight gain velocity have independent or interactive effects on deciduous teeth emergence and overweight status during the first year.

Study design.—Monthly measures of anthropometry and teeth eruption were collected during 1-year trial (0.5–12.5 months) on formula-fed (FF) infants in which the type of randomized infant formula (cow milk or extensively hydrolyzed protein) diet significantly affected early (0.5–4.5 months) weight gain velocity. Generalized linear mixed models determined whether early diet and weight gain velocity had independent or interactive effects on timing and pattern of teeth eruption. Data from a trial on breastfed (BF) infants were used to explore effects of breast milk versus infant formula diets on teeth eruption and overweight status at 10.5 months.

Results.—Independent of infant formula diet, velocities of weight gain had direct effects on the age of first deciduous tooth ($P < .04$) and number of erupted teeth over time ($P < 0.002$). Greater velocity of weight gain from 0.5 to 4.5 months caused earlier and more frequent eruption of deciduous teeth from 4.5 to 12.5 months. Exploratory follow-up analyses on the BF and FF diet groups found early weight gain velocity ($P = 0.001$), but not diet or its interaction, had significant effects. Infants in the upper quartile for weight gain velocity had more primary teeth ($P = 0.002$), and a greater proportion of them were overweight ($P < 0.001$) at 10.5 months.

Conclusions.—Faster weight gain accretion forecasted accelerated primary teeth eruption and increased percentage of children who were overweight—risk factors for dental caries and obesity.

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Trial registration.—[Clinicaltrials.gov NCT01700205](https://clinicaltrials.gov/ct2/show/study/NCT01700205) [2012–2015] and [NCT01667549](https://clinicaltrials.gov/ct2/show/study/NCT01667549) [2012–2015]

Keywords

weight gain velocity; deciduous teeth; diet; infant formula; breast milk; developmental milestones; overweight status

Eruption of deciduous teeth is a regulated process that typically begins during the first and ends by the third year of life¹. Although this developmental process is heritable^{2, 3}, metabolic factors during pre- and post-natal life are associated with its timing^{4–6}. Teething delays occur among children with hypothyroidism^{7, 8} or who are undernourished^{9, 10}, and earlier primary and permanent teeth eruption occur among children who were or became obese^{5, 11, 12} or were diabetic¹³. In a prospective, birth cohort study of infants of diverse ethnicities, infant weight gain during the first three months was significantly associated with earlier eruption of the first tooth, whereas teething delays were characteristic of children of older mothers or those born small for gestational age¹⁴.

Consistent with the associations between permanent teeth eruption and childhood obesity^{5, 11}, a study linked the timing of the first deciduous tooth to weight gain in infancy¹⁴, both of which are influenced by many of the same socioeconomic, nutritional, and metabolic conditions or characteristics of the mother-infant dyad^{4–6, 14–18}. Nevertheless, after adjusting for confounders, evidence has confirmed the positive association between rapid weight gain in infancy and higher weight status or adiposity later in life^{15, 19–22}. However, causal links have not been established.

We had the unique opportunity to investigate whether the type of infant diet, patterns of weight gain, or both have independent (causal) or interactive effects on the timing and pattern of deciduous teeth emergence during the first year. The data analyzed come from a randomized controlled trial (RCT) on healthy, formula-fed (FF) infants for whom the experimental diet manipulation—the type of breast milk substitute fed during the first year—produced significant differences in early weight gain velocities²³. Although their weight was within the range of typically growing infants²⁴, the group of infants fed standard cow milk formula (CMF) had significantly greater weight gain velocities (3.9 g/day greater) from 0.5 to 4.5 months than the group fed an isocaloric, extensively hydrolyzed protein formula (EHF), due to both energy intake and loss mechanisms²³. Because the infants were phenotyped monthly for incidence of primary teeth eruption and gross motor milestones, we tested the hypothesis that if early weight gain has direct, causal effects, it should be independent of the type of infant formula diet and specific to teeth eruption. On the other hand, if teeth eruption is dependent on the infants' diet, then the effects of the infant formula group should be independent of or interact with trajectories of early weight gain. Anthropometric and teething data collected during a trial on breastfed (BF) infants²⁵, most of whom never were fed infant formula and were breastfed for at least 10.5 months, were included to explore the effects of breast milk diet on primary teeth eruption, but at the age of 10.5 months only.

Methods

The primary analyses were conducted on data from FF infants who participated in a RCT on the effects of infant formula diet on growth and energy balance from 0.5 to 12.5 months ([Clinicaltrials.gov NCT01700205](https://clinicaltrials.gov/ct2/show/study/NCT01700205))²³. Infants (N=113) were randomized to be fed either CMF (Enfamil™, Mead Johnson Nutrition; Evansville, IN) or an isocaloric EHF (Nutramigen™, Mead Johnson Nutrition; Evansville, IN) for the first year. Each month, infants were weighed and measured in triplicate by research personnel certified in standard anthropometric techniques and who used calibrated pediatric scales (Scale-Tronix, White Plains, NY) and stadiometers (Harpender Infantometer 702; Crymych, Dyfed, UK) that were accurate to 0.001kg and 0.1 cm, respectively. Anthropometric data were normalized to Z-scores using World Health Organization growth standards²⁴ and the velocities of weight (g/d) and length (cm/d) accretion were calculated by dividing the change of weight in grams or length in centimeters by the change of age in days²⁶ during three time periods: 0.5 to 4.5 months, >4.5 to 8.5 months, and >8.5 to 12.5 months.

For the exploratory follow-up analyses, we included data from a group of BF infants (N=97) who participated in a RCT investigating the effects of maternal diet from 0.5 to 4.5 months on infants' vegetable acceptance after weaning ([Clinicaltrials.gov no. NCT01667549](https://clinicaltrials.gov/ct2/show/study/NCT01667549))²⁵. The timing of the 3-day vegetable acceptance test varied because it depended on when mothers chose to introduce complementary solids. However, dyads returned for follow-up visits, one of which occurred at 10.5 months. Using methods identical to those used for the FF infants, anthropometric measures were obtained monthly from 0.5 to 4.5 months and then again at 10.5 months.

Inclusion criteria encompassed, for both trials, infants born at term (37–42 weeks) with birth weights within a range considered typical (2500–4500g)²⁷, and, for the BF trial only, mothers who intended to exclusively breastfeed (with no formula supplementation) for at least four months. Mothers who had gestational diabetes or infants with congenital malformations, systemic or congenital infections, or family history of atopy were excluded. The Office of Regulatory Affairs at the University of Pennsylvania approved all procedures, and informed consent was obtained from each woman prior to study entry.

The intent-to-treat (ITT) RCT cohort of 113 FF infants (CMF group=59; EHF group=54) was diverse in race/ethnicity, education status, and household income (Table I; available at www.jpeds.com)²³, all of which reflect the urban setting in which they live, the county of Philadelphia²⁸. There were no significant differences in birth weights between the CMF (mean: 3292 g, 3181–3402) and EHF (mean: 3304 g, 95% CI: 3187–3421; $P=0.87$) groups. Neither were there significant group differences in baseline anthropometric characteristics, age of introduction to complementary foods; or energy intake from complementary foods up to 11.5 months²³. However, as we reported previously²³ and as shown in Table 1, the type of infant formula fed had significant effects on early weight gain velocity from 0.5 to 4.5 months ($P=0.003$): the CMF group gained 29.5 g/d (95% CI: 28.0–31.0) whereas the EHF group gained 25.7 g/d (95% CI: 23.7–27.8). Weight gain velocity from 4.5 to 12.5 months and length gain velocity during the three time periods were not statistically different between the two infant formula groups (Table 1. As expected²⁹, the comparator group of BF infants

(N=97) differed significantly from the FF group in almost every outcome measured (Table 1) except velocities of weight gain from 0.5–4.5 months (mean: 26.2 g/d, 95% CI: 24.8–27.7).

By design, the two trials resulted in groups that were dichotomous in infant feeding histories: the FF infants were not fed breast milk and the BF infants never or rarely fed infant formula during the time period (0.5–4.5 months) when velocities of weight and length gain were determined, or thereafter. Although the FF groups were exclusively formula fed, breast milk was the exclusive or predominant source of nourishment for the first 4.5 months for the BF group. After 4.5 months, the majority of BF infants continued to be breastfed: 81% were still breastfeeding and 62% had never been fed infant formula when 10.5 months of age.

For the ITT FF groups, mothers were queried and infants were observed monthly by study personnel to verify the following milestones: crawling on hands and knees, sitting up independently, standing without assistance, walking with assistance, and the number and location of each tooth, if any. We defined tooth eruption as its apparent penetration through the overlying gingiva, which was verified by visual inspection of the oral cavity. From these data, we determined the timing of each milestone, defined as the age at the study visit during which it was first observed, and the number, location (e.g., top, bottom) and type (i.e., incisor, molar) of teeth at each monthly visit from 0.5 to 12.5 months. For the BF group, identical methods were used to determine the number of erupted teeth at monthly intervals from 0.5 to 4.5 months and then at 10.5 months.

Descriptive statistics describing characteristics of the FF and BF infant samples used in the primary and follow-up analyses or follow-up analysis only, respectively, are reported. A 2×3 Mixed Design ANOVA compared groupings of FF infants based on the age of the first deciduous tooth with the number and types of erupted teeth at 12.5 months.

To conduct the primary analyses and test the hypotheses, the gradual progression from exploratory data analysis for identifying covariates to modeling proceeded in a highly procedural manner. First, residuals of all variables were tested for normality using the Shapiro-Wilk test. Second, bivariate relationships of age of first tooth, age of first occurrence of gross motor milestones, and number of primary teeth at 12.5 months with maternal (e.g., age, education, body mass index [BMI] at enrollment, household income) or infant (e.g., sex, race/ethnicity, birth weights, anthropometric measures; weight and length gain velocities) characteristics, listed in Table 1, were examined using t-tests for group comparisons and Pearson correlations for continuous associations.

Variables that were significant in the bivariate relationships were then included in the full factorial General Linear Models on the outcomes of age of first tooth eruption and age of first occurrence of each gross motor milestone, and in Generalized Linear Mixed Models (GLMM) on the outcome of cumulative number of teeth over time using a Poisson distribution and log link function. A random intercept and random effect for time were utilized so that trajectories would be permitted to vary across subjects.

For the exploratory follow-up analyses, the sample consisted of the FF infants from the primary analysis plus the group of BF infants. The cross-sectional outcome of number of

erupted teeth at 10.5 months was tested using the model established from the bivariate relationships. Lastly, exploratory analysis also evaluated groupings of infants based on overweight status, defined as $WLZ > 85$ th percentile ($WLZ > 1.0$)³⁰, as an additional outcome at 10.5 and 12.5 months.

Assumptions for all analyses were evaluated and if violated, remedied appropriately. The nominal alpha (0.05) was used for determining significance. Significant interactions among categorical variables were post-hoc tested using the Fisher Least Significance Difference tests. Significant interactions of continuous and categorical variables were followed up by splitting the continuous variable into meaningful groups to illustrate findings. Data were analyzed using Stata/IC version 14.2 (College Station, TX), Statistica version 13.3 (Tulsa, OK), and R version 3.5.2, with a significance criterion set at $P < 0.05$, and were expressed as mean (standard error of mean) in Table 1 or mean (95% CI) otherwise.

Results

Study retention was 81% ($N = 92$) for the FF infants who had data for weight gain velocity (0.5–4.5 months) and 73% ($N = 83$) had data for teeth outcomes at 12.5 months (Figure 1; available at www.jpeds.com). None of the FF infants erupted a tooth prior to 4.5 months, and all but three erupted a tooth by 12.5 months. In all cases, the first tooth was a bottom or top incisor. Grouping infants by the age when their first primary tooth erupted (i.e., 4.5–6.5 months; 7.5–9.5 months; 10.5–12.5 months) and then analyzing the numbers and types (incisors, molars) of erupted teeth at 12.5 months revealed significant effects of age group ($P < 0.001$), tooth type ($P < 0.001$) and age group $\times$ tooth type interaction ($P < 0.001$). As shown in Figure 2, the group of infants who erupted their first primary tooth the earliest (4.5–6.5 months) had significantly more incisors than the 7.5–9.5 month group, who, in turn, had more erupted incisors than the 10.5–12.5 month group (all $P < 0.001$). They also erupted more molars by 12.5 months than the other two groups (all $P < 0.001$), who were not different from each other ($P = 0.63$).

The timing of first deciduous tooth and the number of erupted teeth at the end of the trial differed based on infant formula group. CMF group had more erupted teeth at 12.5 months (mean: 7.1, 95% CI: 6.1, 8.2) than did the EHF group (mean 5.5, 95% CI: 4.7, 6.4; $P = 0.02$) and they tended to erupt their first tooth at an earlier age (mean: 7.7 months, 95% CI: 7.2, 8.2) than the EHF group (mean: 8.3 months, 95% CI: 7.8, 8.9; $P = 0.08$). In addition, bivariate correlations revealed that weight gain velocity from 0.5–4.5 months, but not during later months (> 4.5 –8.5; > 8.5 –12.5 months), negatively correlated with age at first tooth ($P = 0.02$) and positively correlated with number of erupted teeth at 12.5 months ($P = 0.03$). No other dyad characteristics (listed in Table 1) or velocity of gains in length significantly correlated with these teething outcomes. Thus, the only significant relationships identified in our bivariate analyses were early weight gain velocity and infant formula group.

In contrast to the timing of first tooth eruption, there were no significant differences between the infant formula groups in the age when infants began sitting independently ($P = 0.95$), crawling ($P = 0.20$), standing without assistance ($P = 0.08$), or walking with assistance ($P = 0.40$). In addition, early weight gain velocity was not significantly related to the timing

of any of these gross motor milestones (i.e., sitting [$P=0.67$]; crawling [$P=0.58$]; standing without assistance [$P=0.82$]; walking with assistance [$P=0.12$]).

Table 2 summarizes the ANCOVA model findings on the effects of infant formula group, weight gain velocity, and their interaction on the timing of the developmental milestones. When early weight gain velocity was included in the model, infant formula group (CMF, EHF) was no longer significantly associated with age of first tooth ($P=0.24$), nor was their interaction ($P=0.34$), but early weight gain velocity was significant ($P=0.04$). Infant formula treatment group, early weight gain velocity, nor their interaction had any significant effect in any model involving the timing of gross motor milestones.

For the analysis on the cumulative number of erupted teeth from 4.5 to 12.5 months, the GLMM found no significant effects of infant formula group ($P=0.17$) or any of its interactions (group $\times$ time interaction, $P=0.25$; group $\times$ velocity interaction $P=0.27$; group $\times$ velocity $\times$ time interaction, $P=0.32$). Rather, early weight gain velocity ($\beta = 0.06$; 95% CI: 0.023, 0.101; $P = 0.002$), time ($\beta = 0.542$; 95% CI: 0.423, 0.660; $P<0.001$), and their interaction ($\beta = -0.005$, 95% CI: -0.009 , -0.001 ; $P=0.020$) were significant. This interaction suggests that greater velocity of weight gain during the first 4.5 months accelerates the eruption of teeth. Over time, this acceleration will become less pronounced because all will eventually erupt the same number of deciduous teeth.

To further probe this significant interaction, FF infants were categorized based on weight gain velocities into three groups. Those in the $>75^{\text{th}}$ percentile group gained > 30.7 g/d from 0.5 to 4.5 months whereas the $25^{\text{th}}\text{--}75^{\text{th}}$ percentiles group gained 23.2–30.7 g/d and the $<25^{\text{th}}$ percentile group gained < 23.2 g/day. As shown in Figure 3, FF infants in the $>75^{\text{th}}$ percentile group erupted more teeth over time than the others ($P<0.02$). Additionally, a greater proportion of them were categorized as overweight at 12.5 months (80.0% overweight; $N=20$) compared with the $25^{\text{th}}\text{--}75^{\text{th}}$ (28% overweight; $N=43$) and $<25^{\text{th}}$ (10% overweight; $N=20$) percentile ($P<0.001$) groups.

As shown in Figure 1, 80% ($N=78$) of the BF and 75% ($n=85$) of the FF infants were still enrolled at 10.5 months. Although only one BF infant erupted a tooth by 4.5 months, 94% of the BF infants and 91% of the FF infants had erupted at least one tooth by 10.5 months. The distribution of the total number of teeth at 10.5 months was non-normal, therefore a Poisson regression with logit link function was used in lieu of an ANCOVA. We found no significant effect of diet group ($P=0.17$) or diet group $\times$ weight gain velocity interaction ($P=0.15$) on the number of teeth. However, the main effect of early weight gain velocity was significant ($P<0.001$). The results remained the same when we compared the BF group with each FF (CMF, EHF) group separately.

We used the same procedure described above to further probe this significant interaction; FF and BF infants were categorized into three groups based on early weight gain velocities (Figure 4). The group in the $>75^{\text{th}}$ percentile for early weight gain velocity ($N=41$) had more erupted primary teeth ($P=0.002$; Figure 4, A), and a greater proportion of them were overweight ($P<0.001$; Figure 4, B) at 10.5 months compared with the $<25^{\text{th}}$ ($N=40$) and $25^{\text{th}}\text{--}75^{\text{th}}$ ($N=82$) percentile groups.

Discussion

The present findings provide evidence that the timing and pattern of primary teeth eruption during the first year was directly affected by early rapid weight gain and forecasted overweight status several months later. Variation in how fast infants gained weight during the first 4.5 months, but not how fast they grew in length, had significant effects on the age of the first deciduous tooth, that did not generalize to the age of the first occurrence of several gross motor milestones, findings that were consistent with prior associational studies^{14, 31}. In addition to earlier eruption of the first tooth, greater velocity of weight gain from 0.5 to 4.5 months caused more frequent eruption of deciduous teeth from 4.5 to 12.5 months.

For the primary analyses, we focused on data collected during a trial in which FF infants who were randomized to be fed CMF had greater velocities of early weight gain than those randomized to be fed EHF²³. When we focused solely on differences in the eruption of deciduous teeth between the randomized groups, we found that the CMF group tended to erupt their first primary tooth earlier and had more teeth at 1 year than did those randomized to EHF. However, when the statistical models also factored in early weight gain velocity and its interaction with infant formula group, infant formula group did not explain the variation in the timing of the first tooth or cumulative teeth eruption during the first year. Rather, independent of formula group, weight gain velocity occurring prior to any FF infant erupted a tooth, was significantly related to both the timing and patterning of primary teeth eruption. In other words, the effects of being fed different types of infant formulas (CMF, EHF) on teething were secondary to their differential effects on weight gain velocity.

Unlike retrospective and prospective observational studies, which cannot elucidate causal relationships, the utilization of an RCT design in the FF study provided a longitudinal perspective and thus enabled the determination of the effects of infant formula diet, early weight gain velocity and its interaction, while other variables were randomly distributed. The infant formula treatment groups did not differ in mother-infant characteristics known to be associated with the timing of teeth eruption (eg, maternal age, pre-pregnancy weight gain, race/ethnicity, birth weight, maternal BMI)^{4-6, 14, 18}. Although none of these potential confounders related to the teething outcomes and thus were not included in the model, early weight gain velocity—a known associate in the timing of primary dentition eruption¹⁴—predicted the number of erupted teeth over the first year and was independent of infant formula treatment group.

Further support of the hypothesis that weight gain velocity impacts teeth eruption and is independent of diet came from our follow-up exploratory analysis on the FF group studied in the primary analysis and a group of BF infants for whom breastfeeding was exclusive or predominant for the first 4.5 months and for the majority continued for more than 10 months (and without infant formula supplementation). Independent of diet group, early weight gain velocity significantly associated with number of erupted teeth by 10.5 months. Further, BF and FF infants in the >75th percentile for early weight gain velocity not only had more erupted teeth, but also more than two-thirds of them were categorized as overweight at this time.

Although the BF and FF groups were dichotomous in early feeding histories, we acknowledge several limitations. Teething data for the BF group were available for only one age (10.5 months) and did not include the timing of the eruption of the first deciduous tooth or other developmental milestones. The small sample size did not allow us to factor in the many baseline maternal and infant characteristics that significantly differed between the BF and FF groups and are due, in part, to the psychosocial, economic, and demographic influences on mothers' decision to breastfeed or formula feed³². Nevertheless, when the BF infants were included in the exploratory follow-up analyses, the findings were consistent with those obtained from the randomized FF groups alone suggesting that it is not diet *per se* that causes changes teeth eruption, it is how the infants respond to the diet in terms of weight gain. Further, the period of rapid weight gain occurred prior to the eruption of the first deciduous tooth and during the formation and mineralization of the crowns of developing teeth³³.

Taken together with the rich findings from prospective and retrospective studies, the present findings suggest that metabolic factors during early postnatal life can accelerate the cascade of events surrounding primary teeth eruption^{4, 5, 7–9, 11, 13, 14}. Both acceleration in deciduous teeth emergence and higher overweight status at the end of the first year are of concern because of their associations with increased risk for dental caries³⁴ and obesity³⁵—prevalent diseases of childhood. Whether RCT interventions that successfully reduce rapid infancy weight gain³⁶, also alter the timing and patterning of primary teeth emergence and reduce these risks is an important hypothesis yet to be explored.

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Abbreviations:

ANCOVA	analysis of covariance
ANOVA	analysis of variance
BMI	body mass index
BF	breastfed
CI	confidence interval
CMF	cow milk formula
EHF	extensively hydrolyzed protein formula
FF	formula fed
GLMM	generalized linear mixed model

ITT	intention-to-treat
RCT	randomized controlled trial
SEM	standard error of the mean
WLZ	weight-for-length Z score

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*Three mother-infant dyads in the breastfeeding trial who did not complete the primary outcome visit (vegetable acceptance test) returned for follow-up visit at 10.5 months.

Figure 1; online.

Trial profiles: Flow of participants from enrollment at 0.5 months to 12.5 months in the trial on FF infants and to 10.5 months in the trial on BF infants.

Figure 2.

Association between grouping based on age at first tooth eruption and numbers and type (incisors, molars) of erupted deciduous teeth at 12.5 months (mean $\pm$ 95% CI) among FF infants (age group $\times$ tooth type interaction; $P < 0.001$).

Figure 3.

Cumulative number of teeth (y-axis) by percentile category of early weight gain velocity (z-axis) from 4.5 to 12.5 months (x-axis) among FF infants. GLMM revealed significant weight gain velocity ($P=0.002$), time ($P<0.001$) and velocity $\times$ time interaction ($P=0.02$).

A. Deciduous Teeth, 10.5 months

B. Overweight, 10.5 months

Figure 4.

Number of erupted deciduous teeth (A: mean $\pm$ 95% CI) and proportion of infants who were overweight (B) at 10.5 months, by percentile category of early weight gain velocity among FF and BF infants. Higher weight gain velocity (>75th) percentiles associated with more deciduous teeth ($P=0.001$) and greater proportion of overweight children ($P<0.001$).

Table 1.

Dyad characteristics by infant formula treatment groups and by diet groups

Characteristics ^a	Infant Formula Treatment Groups				Diet Groups		
	CMF	EHF	CMF vs EHF, <i>P</i> -value ^b	Combined FF	BF	FF vs BF, <i>P</i> -value ^b	
Number of dyads enrolled	59	54		113	97		
Infants							
Female, <i>n</i> (%)	28 (47%)	29 (54%)	0.51	57 (50%)	50 (52%)	0.87	
Race, <i>n</i> (%)			0.14			<0.001	
Black	35 (59%)	35 (65%)		70 (62%)	31 (32%)		
White	17 (29%)	8 (15%)		25 (22%)	49 (51%)		
Other/more than one race	7 (12%)	11 (20%)		18 (16%)	17 (18%)		
Anthropometry at 0.5 months, Z-scores							
Weight for age (WAZ), 0.5 month	-0.36±0.11	-0.25±0.11	0.49	-0.30±0.1	0.11±0.1	<0.001	
Length for age (LAZ), 0.5 months	-0.49±0.14	-0.46±0.14	0.91	-0.48±0.1	0.11±0.1	<0.001	
Weight for length (WLZ), 0.5 months	-0.26±0.12	-0.12±0.13	0.43	-0.19±0.1	-0.26±0.1	0.62	
Weight gain velocity (g/d) ^c							
0.5–4.5 months	29.5±0.9	25.7±0.9	0.003	27.7±0.7	26.2±0.1	0.10	
>4.5–8.5 months	15.9±0.6	15.2±0.7	0.46				
>8.5–12.5 months	9.0±0.5	10.1±0.5	0.13				
Length gain velocity (cm/d) ^c							
0.5–4.5 months	0.103±0.002	0.103±0.002	0.97	0.102±0.001	0.095±0.001	<0.001	
>4.5–8.5 months	0.056±0.002	0.053±0.002	0.13				
>8.5–12.5 months	0.043±0.002	0.042±0.002	0.76				
Mothers							
Age, years	27.1±0.7	27.0±0.8	0.89	27.1±0.5	30.8±0.5	<0.001	
Body mass index at 0.5 months, kg/m ²	30.7±1.0	31.4±1.1	0.61	31.1 ±0.7	28.3±0.7	0.008	
Primiparous, <i>n</i> (%)	12 (20%)	11 (20%)	1.00	23 (20%)	33 (34%)	0.03	
Household income, <i>n</i> (%)			0.70			<0.001	
<\$35,000	44 (76%)	37 (70%)		81 (73%)	40 (41%)		
\$35,000–75,000	5 (9%)	7 (13%)		12 (11%)	21 (22%)		

Characteristics ^a	Infant Formula Treatment Groups			Diet Groups		
	CMF	EHF	CMF vs EHF, <i>P</i> -value ^b	Combined FF	BF	FF vs BF, <i>P</i> -value ^b
>\$75,000	9 (15%)	9 (17%)		18 (16%)	36 (37%)	
Education level, <i>n</i> (%)			0.21			<0.001
Primary school	12 (20%)	5 (9%)		17 (15%)	5 (5%)	
High school/technical school	32 (54%)	36 (67%)		68 (60%)	32 (33%)	
College degree or higher	15 (26%)	13 (24%)		28 (25%)	60 (62%)	

Note. Values are mean $\pm$ SEM or *n* (%).

Abbreviations: CMF: cow milk formula; EHF: extensively protein hydrolyzed formula; FF: formula fed; BF: breastfed

^aSome values do not sum to total because of missing data: gestational weight gain (FF: *n* = 111; BF: *n* = 96); maternal BMI (FF: *n* = 112; BF: *n* = 96); household income (FF: *n* = 111)

^b*P*Values for main effect of infant formula treatment (CMF vs EHF) or diet (FF vs BF) groups for categorical variables obtained from Pearson chi-squared tests or 1-way ANOVA for continuous variables with group as between-subjects factor. Comparison of CMF and EHF published previously (ref. 23).

^cComparisons of weight and length gain velocities between BF and FF groups could only be made for the 0.5–4.5 month time period since these data were not available for subsequent time periods for the BF group.

Table 2.

Timing of developmental milestones: Effects of infant formula treatment group with significant covariate—early weight gain velocity (0.5–4.5 months)

Outcomes, age in months	<i>P</i> value ^a		
	Infant formula treatment group	weight gain velocity	Infant formula treatment group × weight gain velocity
First tooth eruption ^b	0.24	0.04	0.34
Sits up	0.36	0.74	0.35
Crawls	0.17	0.15	0.11
Walks with assistance	0.71	0.53	0.60
Stands without assistance	0.13	0.17	0.22

^a *P*-values for effects of infant formula treatment group (CMF, EHF), early weight gain velocity (0.5–4.5 months) and their interaction from ANCOVA. All outcomes normally distributed.

^b Three infants had no teeth at 12.5 months