The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on December 18, 2016

Growth of healthy infants and the timing, type, and frequency of complementary foods[1,2]

WHO Working Group on the Growth Reference Protocol and the WHO Task Force on Methods for the Natural Regulation of Fertility

ABSTRACT

Background: Growth patterns of exclusively and predominantly breast-fed infants differ from those of non-breast-fed infants, but less is known about associations among growth patterns and different durations of exclusive breast-feeding and the types and frequency of complementary foods.

Objective: We examined these associations, particularly between 4 and 6 mo of age, using data from a unique longitudinal 7-country study.

Design: Data from the World Health Organization Multinational Study of Breast-feeding and Lactational Amenorrhea on infants living in generally favorable environments were used. Multilevel analyses described growth and the relation between growth and variables related to feeding.

Results: Small differences in growth that were statistically significant but probably not biologically important were noted among infants in whom complementary foods were introduced at different times. Weight gain was more sensitive to feeding frequencies than were gains in length, but the cumulative 10-wk differences were small. The most extreme differences were equivalent to ≈10 centiles of the weight and height distributions at 6 mo of age.

Conclusions: These results do not provide compelling evidence of benefit or risk related to growth and the timing of introduction of complementary foods at any specific time between 4 and 6 mo of age. Thus, postnatal growth appears to not be sensitive to the differential timing of introduction of complementary foods nor to differential types and frequencies of complementary foods in healthy infants living in environments without major economic constraints and low rates of illness. These results, however, may not indicate growth differences in populations living in poor environments. *Am J Clin Nutr* 2002;76:620–7.

KEY WORDS Breast-feeding, infant growth, growth references, infant feeding practices, anthropometry, weight, recumbent length, child health, child nutrition

INTRODUCTION

Differential growth patterns among formula and exclusively and predominantly breast-fed infants was among the major reasons for the World Health Organization (WHO) undertaking a major initiative to develop new growth references for infants and young children (1–2). Typically, infants who are exclusively or predominantly breast-fed for 4–6 mo with continued breast-feeding through the first year appear to grow more rapidly than do formula-fed infants during the first 2–3 mo and less rapidly from 3 to 12 mo (3–5). Less is known, however, about the sensitivity of breast-fed infants' growth patterns to the differential timing of introduction and type of complementary foods (6). This study sought to address 2 questions: *1*) What are the associations between the timing of introduction of complementary foods and growth in weight and length (attained and velocity) in breast-fed infants? and *2*) What are the associations between the type of complementary foods and the frequency of both breast-feeding and complementary foods and growth in weight and length (attained and velocity) in breast-fed infants? The WHO Multinational Study of Breast-feeding and Lactational Amenorrhea (7–9) provided a unique data set to address these questions. Representation from 7 countries from diverse geographic regions was a particularly valuable feature of this data set. Answers to these questions assisted in the selection of the population from whom the new growth reference will be developed and in evaluating the robustness of the reference to the differential timing of introduction of complementary foods after 4 mo of age.

SUBJECTS AND METHODS

Data

The WHO Multinational Study of Breast-feeding and Lactational Amenorrhea was conducted at 7 sites (Chengdu, China; New Delhi; Guatemala City; Sagamu, Nigeria; Santiago, Chile; Uppsala, Sweden; and Westmead, Australia) from April 1989 to December 1992. Five to seven hundred women and newborns were recruited at each site through government or private or university hospitals, except in Chengdu, where women in rural townships were recruited by a government research institute (7). Entry criteria required that women intended to breast-feed for ≥6 mo, breast-fed a previously born infant for ≥4 mo, and were between 20 and 37 y of age, parous, literate, and of normal nutritional status (ie, neither obviously malnourished nor obese on the basis of local criteria). Women were excluded if the gestational age of their newborn was <37 wk or if they used contraception immediately after delivery. All study sites except Chengdu were urban, and the median educational levels of participating mothers were high

[1] From the Department of Nutrition (World Health Organization Working Group) and the United Nations Development Program/United Nations Fund for Population Activities/World Health Organization/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (World Health Organization Task Force), World Health Organization, Geneva.

[2] Address reprint requests to M de Onis, Department of Nutrition, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. E-mail: deonism@who.ch.

Received March 28, 2001.

Accepted for publication September 18, 2001.

 © 2002 American Society for Clinical Nutrition

(9). The populations were ethnically homogeneous at each site, except in Westmead (9). The study infants were healthy singletons with a weight-for-age at the time of entry into the study of ≥ 10 centile of the local standard (or ≥ 2500 g if a local standard was not available).

Enrollment occurred between 72 h and 7 d after delivery. The obstetric and breast-feeding history, education level, socioeconomic status, and standing height of the mothers were ascertained at enrollment. The weights and lengths of the infants were also measured at that time, on average at 5 d (7). Each mother-infant pair was visited at home every 2 wk until the mother experienced 2 consecutive normal menstruations or became pregnant. The infant's weight was measured at each visit, and length was measured fortnightly (Chengdu, Santiago) or monthly (all other sites). The mothers were asked whether the infants had any episodes of illness in the past 2 wk and, if so, further information was obtained about diarrhea, respiratory infection, and other illnesses. The infants' feeding status was ascertained at each visit from daily food records kept by the mothers. Feeding status was categorized at each visit as *1*) exclusive breast-feeding, *2*) predominant breast-feeding (breast milk + non-energy-containing liquids + other foods as tastes only), *3*) partial breast-feeding (breast-milk + energy-containing liquids or foods) or, *4*) weaned (ie, no longer breast-fed). The duration of exclusive and predominant breast-feeding was determined on the basis of the visit with the first transition to a different feeding status. The median duration of exclusive breast-feeding was 1 wk in Guatemala City, Santiago, Sagamu, and New Delhi; 6 wk in Uppsala and Westmead; and 10 wk in Chengdu (7). The median duration of predominant breast-feeding was 1 wk in Guatemala City, Santiago, and Sagamu; 11 wk in New Delhi; 15 wk in Uppsala and Westmead; and 27 wk in Chengdu. The protocol was approved by the WHO and the participating institutions.

Statistical analyses

Data related to specific sites, individual infants, and the timing of selected feeding milestones served as distinct sources of potential variability and explanatory power. Thus, multilevel modeling was implemented in SAS PROC MIXED, version 6.12 (10). This procedure accommodates categorical and continuous covariates, incomplete series of time measurements, and the added variability introduced by the multiple levels represented by sites, individuals, and time.

The assessment of and adjustment for potential selection biases due to loss to follow-up was an important analytic issue. It was particularly important, for example, to account for differences in the growth of infants born to women with short compared with long durations of lactational amenorrhea. Thus, the analyses were done for subsets of mother-infant pairs with a specified minimum follow-up, and the time of discontinuation was included as a covariate in completely separate analyses. This approach was shown previously to account for selection bias effects (11).

Timing of introduction of complementary foods and growth

Data were available for 1252 predominantly (including exclusively) breast-fed infants from 5 sites who were followed for ≥ 32 wk to examine the association of the timing of introduction of complementary foods with infant length and weight for weeks 1–16 and 17–32. The number of Guatemalan and Nigerian infants with a sufficiently long duration of predominant breast-feeding was too small for these analyses. There were not sufficient numbers of infants with a long duration of exclusive breast-feeding to conduct a similar analysis on the timing of exclusive breast-feeding.

Growth curves for each infant were generated by using random-coefficient modeling. This modeling incorporated categorical and continuous covariates that might influence infant growth, accounted for missing growth measurements, and estimated the variability among infants in attained growth, growth velocity, and time of measurement, after the covariates were accounted for. Preliminary analyses indicated that a quadratic or cubic polynomial were the maximum orders needed to describe the shape of growth curves. For most analyses, however, a straight line was adequate to capture differences between the feeding groups.

Separate analyses were conducted for each of 2 periods: 1–16 and 17–32 wk. For each period, the associations between the timing of introduction of complementary foods and growth characteristics are reported as differences in growth attained at the middle of the designated period (ie, in mm or g) and in the rate of change over the entire designated period (ie, velocity in mm/wk or g/wk). For the 17–32 wk period, attained growth was adjusted for the growth attained during the 1–16-wk period. Estimates for the intervals 1–8, 9–16, or 25–32 wk were compared with those obtained for 17–24 wk. The analyses were stratified by sites, and the results were combined across sites, weighting for sample sizes and random variation among sites. This procedure accounted for potential site differences in the patterns of breast-feeding and introduction of complementary foods. Separate analyses for each site also permitted the modeling of 2 (ie, individuals and time) rather than 3 levels of variability, which substantially reduced model complexity.

Type and frequency of complementary foods and breast-feeding

Growth measurements were adjusted for previous growth performance and selected covariates. This approach is useful for studying the associations of time-varying covariates such as breast-feeding frequency or past illness. Two subsets of infants from all 7 sites were included: 751 and 205 infants who were breast-fed predominantly and exclusively, respectively, to ≥ 16 wk. Data from weeks 1–8, 9–16, 17–24, and 25–32 were analyzed separately; 4-wk increments for length and 2-wk increments for weight were estimated. Length and weight gains were regressed on means of covariates estimated from observations at the beginning of designated intervals and the 2 wk before these intervals.

Preliminary analyses showed that variables specific to individual infants (eg, birth weight and mother's height) and sites were not important determinants of changes in growth. These influences were accounted for by adjustments for previous growth performance. Therefore, growth increments for all infants and sites were combined (ie, pooled) into a single multiple linear regression. Breast-feeding frequency, ie, the average number of total breast-feedings per day for the designated interval, was included in each regression analysis.

Several other covariates were included in these regression analyses. Covariates for feeding frequencies of non-energy-containing fluids, milk fluids, other energy-containing fluids, and solids and semisolids (average number of feedings per day) were included as permitted by the distributions of the frequencies. The age of the infant (in wk) and the age at the time of discontinuation from the study were included to control for age differences in growth velocity and for effects related to the length of follow-up. The illnesses of the infants were included to examine the association of previous illnesses with subsequent growth velocity. Illness was defined as 0 if illness occurred in neither of the previous 2-wk periods, 0.5 if any illness occurred in one of the previous 2-wk periods, and 1 if any illness occurred in both periods.

The American Journal of Clinical Nutrition
Downloaded from ajcn.nutrition.org by guest on December 18, 2016

TABLE 1
Description of the predominantly (including exclusively) breast-fed sample at enrollment to the study

	Site				
	Uppsala (n = 299)	Westmead (n = 366)	Chengdu (n = 195)	Santiago (n = 255)	New Delhi (n = 137)
Mothers					
Age (y)	30.9 ± 3.4[1]	31.1 ± 3.2	27.9 ± 3.8	26.4 ± 4.0	25.6 ± 3.0
Education level (y)	14.6 ± 2.8	14.6 ± 2.6	5.5 ± 1.8	9.9 ± 2.5	9.5 ± 4.0
Duration of previous predominant breast-feeding (mo)	4.9 ± 1.5	5.3 ± 1.5	8.3 ± 3.9	4.1 ± 3.2	5.3 ± 2.1
Pregnancy duration (wk)	39.7 ± 1.2	39.9 ± 1.1	39.8 ± 1.1	39.5 ± 1.2	39.1 ± 1.3
Home delivery (yes/no)	—[2]	—	0.66	—	—
Good general health (yes/no)	0.79	0.87	—	0.68	—
Smoking daily (yes/no)	—	—	—	0.158	—
Alcohol use (yes/no)	0.60	0.67	0.08	0.26	—
Recreational drug use (yes/no)	—	0.14	—	—	—
Height (cm)	167.5 ± 5.7	164.7 ± 6.2	154.0 ± 4.3	155.1 ± 5.1	154.2 ± 4.6
Weight (kg)	66.7 ± 8.0	66.9 ± 9.7	51.0 ± 5.2	59.4 ± 4.6	49.9 ± 6.9
Supplement use (yes/no)	0.12	0.27	—	0.74	—
Newborns[3]					
Interval between delivery and start of breast-feeding (h)	1.0 ± 0	0.8 ± 1.5	40.0 ± 20.1	7.3 ± 3.4	6.4 ± 5.6
Total breast feedings (no./d)	11.6 ± 6.9	9.2 ± 8.6	9.9 ± 2.6	13.2 ± 7.9	13.0 ± 2.7
Pacifier use (yes/no)	0.79	0.32	0.14	0.20	—
Breast problems since delivery (yes/no)	0.41	0.57	0.02	0.27	—
Food or fluid given since start of breast-feeding (yes/no)	0.37	0.31	0.35	0.49	0.42
Female infant (yes/no)	0.44	0.46	0.41	0.46	0.40
Infant weight (kg)	3.75 ± 0.42	3.63 ± 0.47	3.36 ± 0.37	3.42 ± 0.39	3.00 ± 0.39
Infant length (cm)	51.8 ± 1.7	51.8 ± 2.1	49.2 ± 2.0	50.8 ± 1.7	49.7 ± 2.1
Infant head circumference (cm)	35.9 ± 1.2	35.5 ± 1.4	33.6 ± 1.4	35.2 ± 1.8	34.3 ± 1.3
Infant chest circumference (cm)	35.8 ± 1.8	35.8 ± 4.1	32.8 ± 1.8	34.5 ± 2.1	33.1 ± 1.7
Maternal arm circumference (cm)	27.4 ± 2.5	27.4 ± 3.0	24.0 ± 1.8	24.6 ± 1.6	23.1 ± 2.0

[1] $\bar{x}$ ± SD.
[2] Means and proportions were not included in the table when they were essentially zero.
[3] Between 72 h and 7 d after delivery, on average at 5 d.

RESULTS

Description of sample

Selected characteristics of the 1252 mothers who predominantly (including exclusively) breast-fed their infants and were followed for ≥32 wk are shown in **Table 1**; this sample was used to determine the associations between the timing of introduction of complementary foods and growth in weight and length (attained and velocity) in the breast-fed infants. Means and proportions that were essentially zero were not included in the table. The different geographic sites provided considerable diversity among the factors of interest. Maternal education was highest in Uppsala and Westmead. The duration of previous predominant breast-feeding was highest in Chengdu. Smoking was frequent only in Santiago, and alcohol use was frequent in Uppsala, Westmead, and Santiago. Recreational drug use was reported only in Westmead. The frequency of breast-feedings was lowest in Westmead and Chengdu. Pacifier use at enrollment was highest in Uppsala. Maternal height and weight were highest in Uppsala and Westmead. Infant weight at enrollment was highest in Uppsala and Westmead and lowest in New Delhi; enrollment lengths were highest in Uppsala and Westmead and lowest in Chengdu. The proportions of females were lowest in Chengdu and New Delhi. Most of the women at all sites breast-fed on demand. The interval between delivery and the start of breast-feeding was long in Chengdu; in both Chengdu and Santiago, almost all of the infants were given some food or fluid before the first breast-feeding (7). Throughout the period of follow-up, breast-feeding frequencies were lowest in Uppsala and Westmead, primarily because of a lower frequency of night feedings. At the other 3 sites, nearly all of the women provided unrestricted access to the breast at night. The frequency of non-energy-containing and milk feedings was highest in New Delhi. The frequency of energy-containing feedings was highest in Santiago. The frequencies of solid foods was highest in Westmead and lowest in Chengdu. The proportion of women working outside the home was highest in Uppsala and Westmead (data not shown). Unadjusted average values for attained weight derived from observations between 1 and 16 wk were lowest in New Delhi; infant length for the same period was lowest in Chengdu (data not shown). Reported illnesses were lowest in Chengdu; respiratory illnesses (ie, cold, runny nose, and cough) were more common than was diarrhea at all sites (data not shown). The 2-wk incidence of diarrhea was low, being <6% at all sites except New Delhi (11%; data not shown).

Enrollment factors were similar between those subjects included (n = 1252) and those excluded (n = 1649) from these analyses with one exception. The maternal weight of the included sample was 0.4–2.6 kg less (depending on site) than that of the sample excluded from these analyses.

Timing of introduction of complementary foods and growth

The mean length and weight attained during the 1–16-wk study period were smaller in infants whose complementary feeding was initiated before 17–24 wk than in those whose complementary feeding was initiated between 17 and 24 wk (**Table 2**). The mean length velocity was smaller only at weeks 1–8, whereas the mean weight

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on December 18, 2016

TABLE 2
Differences in the length and weight of infants relative to the time of introduction of complementary foods averaged across 5 sites over 1–16 and 17–32 wk after birth[1]

Growth measure	Time of introduction of complementary foods	Difference	SE	P[2]
	wk			
1–16 wk[3]				
Attained length (mm)	1–8	−1.803	0.311	0.001
	9–16	−2.368	0.278	0.001
	25–32	−0.650	0.924	0.564
Length velocity (mm/wk)	1–8	−0.192	0.080	0.049
	9–16	0.010	0.071	0.908
	25–32	−0.021	0.039	0.659
Attained weight (g)	1–8	−47.1	21.2	0.068
	9–16	−56.6	15.0	0.002
	25–32	38.8	37.6	0.397
Weight velocity (g/wk)	1–8	−1.7	2.19	0.524
	9–16	−6.8	2.55	0.029
	25–32	2.1	2.09	0.410
17–32 wk[4]				
Attained length (mm)	1–8	0.902	0.443	0.095
	9–16	1.486	0.283	0.001
	25–32	0.459	0.917	0.681
Length velocity (mm/wk)	1–8	0.004	0.032	0.918
	9–16	−0.116	0.106	0.369
	25–32	−0.151	0.038	0.001
Attained weight (g)	1–8	49.6	18.5	0.028
	9–16	51.6	16.8	0.012
	25–32	19.8	20.9	0.437
Weight velocity (g/wk)	1–8	3.0	1.17	0.035
	9–16	2.2	2.25	0.423
	25–32	−3.6	2.65	0.265

[1] n = 1252. Differences in attained growth were estimated at the midpoint of the time period (ie, distance in mm and g) for groups to whom complementary foods were introduced during 1–8 (n = 471), 9–16 (n = 243), or 25–32 (n = 173) wk compared with during 17–24 wk (n = 365).

[2] Adjusted for multiple comparisons for each growth measure by applying Bonferroni's inequality.

[3] Models were fit for each site separately and then the differences were combined. Covariates in the models, if there was sufficient variability in a particular site, were as follows: maternal age; duration (y) of mother's education; previous surgery in mother (yes or no); number of previous births; duration (mo) of full breast-feeding of previously born infant; duration of pregnancy; mother's health generally good (yes or no); assistance with breast preparation (yes or no); mother's use of alcohol, drugs, or micronutrient supplements (yes or no); number of times meat was eaten by mother per week; mother's height and weight; home delivery of infant (yes or no); medication use during or after delivery (yes or no); pregnancy complications (yes or no); time interval before first breast-feeding; food given to infant before first breast-feeding (yes or no); unrestricted access by infant to the breast (yes or no); total number of breast-feedings per day; infant's use of a pacifier (yes or no); breast problems (yes or no); and sex of infant.

[4] Covariates in the models, in addition to those covariates listed above, were the average of the following factors measured during weeks 1–16 of follow-up: infant length and weight; maternal and infant illness; frequency of intercourse, smoking, alcohol drinking, drug use, and working out of the home; unrestricted access by infant to the breast; expression of breast milk; numbers of breast-feedings, noncaloric feeds, milk or formula feeds, caloric feeds, and solid food feeds; pacifier use; eating meat by mother; and maternal micronutrient supplementation.

velocity was smaller only at weeks 9–16. Although statistically significant (the CIs for these differences did not overlap zero), the maximal differences in the groups' attained weights, lengths, and growth velocities were small (≈2 mm for attained length, ≈50 g for attained weight, ≈0.2 mm/wk for length velocity, and ≈7 g/wk for weight velocity). Infants in whom complementary foods were introduced between 25 and 32 wk did not differ significantly in weight and length (distance and velocity) from infants in whom complementary foods were introduced between 17 and 24 wk.

During the 17–32-wk period (adjusted for growth in the previous period), infants introduced to complementary foods before 17–24 wk were ≈1 mm longer and 50 g heavier and had a slightly higher weight velocity during weeks 1–8 than did infants introduced to complementary foods between 17 and 24 wk. Attained length or weight and weight velocity were not significantly different between infants who had complementary foods introduced between 25 and 32 wk and those who had complementary foods introduced between 17 and 24 wk, but the former group had a slightly lower length velocity (0.15 mm/wk).

Type and frequency of complementary foods and breast-feeding

Infants predominantly breast-fed for ≥16 wk

The associations of breast-feeding frequency, frequency of non-energy-containing fluids, infant age, and infant illness with the length and weight velocities of the infants who were predominantly breast-fed for ≥16 wk are shown in **Table 3**. Across the periods 1–8, 9–16, 17–24, and 25–32 wk, associations of age with length and weight gain were negative and decreased in magnitude. Associations of illness, breast-feeding, and frequency of non-energy-containing fluids with both length and weight velocities during 1–8 wk were not significant.

A higher frequency of illness was associated with higher mean length velocity during 9–16 wk, but the magnitude of the association was small. The difference in length velocity between infants

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on December 18, 2016

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on December 18, 2016

TABLE 3
Associations of length and weight velocities with breast-feeding frequency, frequency of non-energy-containing and other fluids, age, and illness in infants who were breast-fed predominantly for ≥16 wk[1]

	Length velocity (mm/wk)		Weight velocity (g/wk)	
	Coefficient	P	Coefficient	P
Weeks 1–8				
Constant	11.767	0.000	262.541	0.000
Age (wk)	−0.771	0.023	−15.614	0.000
Illness	0.067	0.868	0.550	0.941
Breast-feeding frequency	−0.039	0.453	0.077	0.937
Frequency of non-energy-containing fluids	−0.155	0.550	1.305	0.797
Weeks 9–16				
Constant	6.490	0.000	148.843	0.000
Age (wk)	−0.229	0.000	−6.626	0.000
Illness	0.771	0.003	−3.515	0.469
Breast-feeding frequency	0.040	0.326	1.401	0.058
Frequency of non-energy-containing fluids	0.028	0.863	5.138	0.090
Weeks 17–24				
Constant	4.855	0.000	120.649	0.000
Age (wk)	−0.106	0.009	−3.060	0.000
Illness	−0.862	0.000	−11.376	0.015
Breast-feeding frequency	0.002	0.958	0.129	0.875
Frequency of non-energy-containing fluids	−0.131	0.247	−4.900	0.042
Weeks 25–32				
Constant	2.727	0.000	109.520	0.000
Age (wk)	0.012	0.756	−3.361	0.000
Illness	−0.163	0.418	−7.669	0.124
Breast-feeding frequency	−0.020	0.601	−1.863	0.044
Frequency of non-energy-containing fluids	−0.053	0.523	−1.428	0.488
Frequency of milk fluids[2]	0.144	0.309	0.986	0.802
Frequency of energy-containing fluids[2]	0.006	0.981	−7.518	0.318
Frequency of solid foods[2]	0.341	0.001	0.457	0.871

[1] n = 751. Differences in velocity of length and weight associated with the covariates were obtained through multiple linear regression. The table presents unstandardized regresssion coefficients and corresponding P values. The unit for each of the feeding covariates (ie, breast-feeding, non-energy-containing fluids, milk fluids, energy-containing fluids, and solid foods) was the number of feedings per day, so the regression coefficients for these covariates represent the differences in length or weight velocity associated with an additional feeding per day. Illness was coded 0 if the illness occurred in neither of the previous 2-wk periods, 0.5 if any illness occurred in one of the previous 2-wk periods, and 1 if any illness occurred in both periods.

[2] Sufficiently frequent to be included in the analysis.

with no illness and those who were ill in both previous 2-wk periods was 0.8 mm/wk. Length velocity during that period was not associated with either breast-feeding patterns or the frequency of use of non-energy-containing fluids. Weight velocity was not associated with frequencies of illness, breast-feeding, or feeding of non-energy-containing fluids during 9–16 wk.

Between 17 and 24 wk, a higher frequency of illness was associated with both lower length and lower weight velocities (−0.9 mm/wk and −11.4 g/wk, respectively) and a higher feeding frequency of non-energy-containing fluids was associated with a lower weight velocity (−4.9 g/wk per additional feeding per day). Only the frequency of solid foods was associated positively with length velocity between 25 and 32 wk (0.3 mm/wk per additional feeding per day). For weight, only breast-feeding frequency was associated negatively with weight velocity.

Infants exclusively breast-fed for ≥16 wk

The associations of frequency of feeding, infant age, and illnesses with the length and weight velocities of infants who were breast-fed exclusively for ≥16 wk are shown in **Table 4**. Across the periods 1–8, 9–16, 17–24, and 25–32 wk, the associations of age with weight velocities were negative and progressively decreased, becoming less negative. This pattern was not observed for length.

Only a higher rate of illness in the preceding 2–4 wk was associated with a higher subsequent length velocity during 1–8 wk (a difference of 1.7 mm/wk between those with some illness in both previous periods and those with no illness in either period). A higher number of illnesses during the preceding 2–4 wk was associated with a lower weight velocity during weeks 17–24 and 25–32 (−27.2 and −20.1 g/wk, respectively). Only a higher frequency of use of energy-containing fluids was associated with lower weight gains (−21.0 g/wk per additional feeding per day) during 25–32 wk.

The percentages of the variability in weight or length velocity explained by these regression models were small, ranging between 1% and 6%. The SDs of the residuals after the covariates were accounted for ranged from 2.3 to 3.4 mm/wk for length and from 79 to 97 g/wk for weight.

DISCUSSION

This study is the first international comparison—using data collected according to a common protocol—of the relations between the growth of breast-fed infants in several continents and the timing, type, and frequency of complementary foods. Small significant differences in growth were observed between infants in

TABLE 4
Associations of length and weight velocities with breast-feeding frequency, frequency of non-energy-containing and other fluids, age, and illness in infants who were breast-fed exclusively for ≥16 wk[1]

	Length velocity (mm/wk)		Weight velocity (g/wk)	
	Coefficient	*P*	Coefficient	*P*
Weeks 1–8				
Constant	5.772	0.090	234.137	0.000
Age (wk)	−0.256	0.684	−16.489	0.000
Illness	1.673	0.032	18.669	0.225
Breast-feeding frequency	0.107	0.264	2.650	0.159
Weeks 9–16				
Constant	6.306	0.000	196.875	0.000
Age (wk)	−0.296	0.000	−6.959	0.000
Illness	0.406	0.367	−8.825	0.366
Breast-feeding frequency	0.073	0.271	−1.104	0.427
Weeks 17–24				
Constant	5.197	0.000	136.105	0.000
Age (wk)	−0.096	0.150	−4.245	0.003
Illness	−0.739	0.076	−27.195	0.005
Breast-feeding frequency	−0.047	0.481	−1.275	0.454
Weeks 25–32				
Constant	3.361	0.000	117.958	0.000
Age (wk)	−0.072	0.264	−2.568	0.067
Illness	−0.666	0.075	−20.115	0.033
Breast-feeding frequency	−0.005	0.936	−1.010	0.503
Frequency of non-energy-containing fluids	−0.338	0.234	−3.934	0.598
Frequency of milk fluids[2]	−0.126	0.760	−6.650	0.550
Frequency of energy-containing fluids[2]	−0.051	0.892	−21.042	0.045
Frequency of solid foods[2]	0.065	0.749	−7.084	0.202

[1] $n = 205$. Differences in velocity of length and weight associated with the covariates were obtained through multiple linear regression. The table presents unstandardized regresssion coefficients and corresponding *P* values. The unit for each of the feeding covariates (ie, breast-feeding, non-energy-containing fluids, milk fluids, energy-containing fluids, and solid foods) was the number of feedings per day, so the regression coefficients for these covariates represent the differences in length or weight velocity associated with an additional feeding per day. Illness was coded 0 if the illness occurred in neither of the previous 2-wk periods, 0.5 if any illness occurred in one of the previous 2-wk periods, and 1 if any illness occurred in both periods.

[2] Sufficiently frequent to be included in the analysis.

whom complementary foods were introduced at different times between 4 and 6 mo of age. These differences, however, were too small to be of likely biological significance. The most extreme differences among the various groups whose growth was compared were equivalent to ≈10 centiles of growth distribution at 6 mo of age. Thus, these results do not provide any compelling evidence of benefit or risk related to growth and the timing of introduction of complementary foods at any specific time between 4 and 6 mo of age in infants who are healthy, live in environments without major economic constraints, and have low rates of illness. In these populations, postnatal growth does not appear to be sensitive to the differential timing of introduction of complementary foods. These results should not be extrapolated to populations who live in environments less supportive of physical growth. However, the results do support the expectation that growth references derived from healthy populations who exclusively or predominantly breast-feed their children up to ≥4 mo of age should not be affected by the differential timing of introduction of complementary foods thereafter.

Although the study's design precludes assigning causative relations, the large sample size and intense longitudinal follow-up provided sufficient statistical power to estimate the magnitude of associations between feeding practices and growth in both short- and longer-term intervals while multiple possible confounding factors and selection effects (12)—such as site, previous growth performance, maternal size, and socioeconomic status (SES)—are controlled for. Control for previous growth is especially important to minimize the likelihood of 2 potential sources of bias, reverse causality and regression to the mean (13).

These results agree with those found in the literature. Most previous studies differ from this one in that they targeted infants from lower SES groups who had greater exposures to infectious agents (13–20). In the available studies, expected growth differences at 4–6 mo of age among groups introduced to complementary foods at different ages should vary with the group's SES status and exposure to infectious illness. That is, the less favorable a group's SES status and the more likely its infectious disease exposure, the greater is the expected growth difference among feeding groups. The less favorable the circumstances, the greater is the expected protection of growth by predominant or exclusive breast-feeding. This is consistent with the underlying biology of lactation and the protection that breast-feeding affords infants (21).

A controlled trial that assessed the relation between growth and complementary feeding practices also provides evidence in line with our results (22). Conducted in a population with a lower SES than that in the present study, the results showed small, nonsignificant differences in monthly length and weight gains associated with longer exclusive breast-feeding between 4 and 6 mo of age. The absence of growth differences between the partial and exclusive breast-feeding groups between 4 and 6 mo, in contrast with what would have been expected given the population demographics, is explained by the preprepared commercial baby foods used to avoid the potential influ-

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on December 18, 2016

ence of higher morbidity or nutrient deficiency in the infants who received solid foods.

The data set used also provided significant advantages in assessing relations between growth and the type of complementary feeding and its frequency and that of breast-feeding. Although our analytic approach did not eliminate the possibility of all bias from reverse causality, it did minimize this concern substantially. Nonetheless, we have seen mixed results; some are consistent with the known biology of feeding, whereas others are more difficult to interpret. For example, one would expect to see effects on weight velocity before effects on length velocity because the former is likely a more acute effect and would be easier to detect. This was what we observed. Neither the frequency of breast-feeding nor the feeding of complementary foods was associated significantly with length velocity in any of the 4 periods examined in infants who were either predominantly or exclusively breast-fed for ≥16 wk, with one notable exception. The frequency of feeding solid foods was associated positively with length velocity, but not with weight velocity during weeks 25–32 in infants who were predominantly breast-fed for ≥16 wk. It is difficult to explain both findings parsimoniously; thus, one must be cautious in interpreting these results.

Caution is suggested by other inconsistent findings related to weight velocity. Negative associations between weight velocity and the frequency of feeding non-energy-containing fluids were observed in weeks 17–24 and between weight velocity and the frequency of breast-feeding in weeks 25–32 in infants who were predominantly breast-fed for ≥16 wk. Had feeding non-energy-containing fluids influenced weight gain by interfering with breast-feeding, a relation between breast-feeding frequency and weight gain might be anticipated. This was not observed. Similarly, among the infants exclusively breast-fed for ≥16 wk, the only significant association was a negative one between the frequency of feeding energy-containing fluids and weight velocity in weeks 25–32. However, weight velocity and the frequency of feeding solid foods were not significantly associated.

Difficulties in interpreting these data reflect that feeding frequencies may be an inadequate indicator of the quantity and quality of what the infant is being fed. The published literature offers similarly conflicting data (23–25). In most cases, either the potential of reverse causality is a major limitation or there is inadequate information regarding quality, quantity, or frequency. These limitations are exacerbated by the strong likelihood that an increase in the consumption of energy-containing complementary foods decreases the consumption of human milk (19, 22). Gaining further understanding about possible influences of the type, frequency, quantity, and quality of complementary foods on growth will be challenging because an adequate sample of infants whose intake of breast milk and complementary foods is measured in detail frequently over time is needed.

An international effort initiated and coordinated by the WHO is under way to develop a new growth reference (1). The goal is to collect longitudinal data from a large sample of infants who are breast-fed throughout the first year of life, live in healthy environments that do not limit their genetic growth potential, and represent a diversity of ethnic and racial backgrounds (26). At the time of this writing, data collection is under way in 6 countries (Brazil, Ghana, India, Norway, Oman, and United States) representing all of the major world regions. The new World Health Organization growth reference will include data from birth to 5 y of age, based on longitudinal data from 0 to 24 mo and cross-sectional data thereafter. The new reference is envisioned to be available in the year 2005.

These results were produced as part of the preparatory work for this endeavor and indicate that postnatal growth in length and weight is not sensitive to the differential timing of introduction of complementary foods or the type and frequency of complementary foods. This study evaluated these factors among mother-infant pairs from populations that were generally healthy, living in good environments, and had low rates of illness. The results are highly applicable to the protocol for the new international growth reference but may not indicate how these factors affect growth in environments with high levels of microbiological contamination.

Manuscript preparation: Edward Frongillo, Mercedes de Onis, and Cutberto Garza.

The members of the WHO Working Group on the Growth Reference Protocol are as follows: Mercedes de Onis (WHO, Geneva), Edward A Frongillo (Cornell University, Ithaca, NY), Cutberto Garza (Chairman; United Nations University, Ithaca, NY), CG Victora (Universidade Federal de Pelotas, Pelotas, Brazil), T J Cole (Institute of Child Health, London), N Cameron (Loughborough University, Leicestershire, United Kingdom), M Shekar (UNICEF, Dar es Salaam, Tanzania), and R Yip (UNICEF, Beijing).

The members of the WHO Task Force on Methods for the Natural Regulation of Fertility are as follows. *Principal investigators and centers:* S Bhatnagar (National Institute of Health and Family Welfare, New Delhi), H Burger (Prince Henry's Institute of Medical Research, Clayton, Australia), HL Delgado (Institute of Nutrition of Central America & Panama, Guatemala City), OA Dada (Department of Pathology, Ogun State University, Sagamu, Nigeria), B Gross (Department of Medicine, Westmead Hospital, Westmead, Australia), Y Hofvander (Department of Paediatrics, Uppsala University, Uppsala, Sweden), PA Lavin (Department of Obstetrics and Gynaecology, University of Chile, Santiago), Tang Guang-hua (Family Planning Research Institute of Sichuan, Chengdu, People's Republic of China). *Study design and monitoring:* PFA Van Look, H von Hertzen, O Ayeni, and A Glasier (Department of Obstetrics & Gynaecology, University of Edinburgh, United Kingdom) and the Steering Committee of the Task Force on Methods for the Natural Regulation of Fertility (UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, Geneva). *Data coordination and statistical analysis:* O Ayeni; APY Pinol, AJM Chevrot, M Vucurevic, and VS Nagi (UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction).

REFERENCES

1. de Onis M, Garza C, Habicht J-P. Time for a new growth reference. Pediatrics [serial online] 1997;100:e8. Internet: http://www.pediatrics.org/cgi/content/full/100/5/e8 (accessed 11 June 2002).
2. World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser 1995;854:161–262.
3. World Health Organization Working Group on Infant Growth. An evaluation of infant growth. Geneva: World Health Organization, 1994.
4. World Health Organization Working Group on Infant Growth. An evaluation of infant growth: the use and interpretation of anthropometry in infants. Bull World Health Organ 1995;73:165–74.
5. Dewey KG. Growth characteristics of breast-fed compared to formula-fed infants. Biol Neonate 1998;74:94–105.
6. Frongillo EA, Habicht JP. Investigating the weanling's dilemma: lessons from Honduras. Nutr Rev 1997;55:390–5.
7. World Health Organization Task Force on Methods for the Natural Regulation of Fertility. The World Health Organization Multinational Study of Breast-feeding and Lactational Amenorrhea: I. Description of infant feeding patterns and of the return of menses. Fertil Steril 1998;70:448–60.

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on December 18, 2016

8. World Health Organization Task Force on Methods for the Natural Regulation of Fertility. The World Health Organization Multinational Study of Breast-feeding and Lactational Amenorrhea: II. Factors associated with the length of amenorrhea. Fertil Steril 1998;70: 461–71.
9. World Health Organization Working Group on the Growth Reference Protocol and World Health Organization Task Force on Methods for the Natural Regulation of Fertility. Growth patterns of breastfed infants in seven countries. Acta Paediatr 2000;89: 215–22.
10. SAS Institute Inc. Changes and enhancements, release 6.07. Cary, NC: SAS Institute Inc, 1992. (SAS Technical Report P-229.)
11. Wu MC, Bailey KR. Estimation and comparison of changes in the presence of informative right censoring: conditional linear model. Biometrics 1989;45:939–55.
12. Frongillo EA, Rowe EM. Challenges and solutions in using and analyzing longitudinal growth data. In: Johnston FE, Eveleth P, Zemel B, eds. Human growth in context. London: Smith-Gordon, 1999:51–64.
13. Victora CG, Morris SS, Barros FC, Horta BL, Weiderpass E, Tomasi E. Breast-feeding and growth in Brazilian infants. Am J Clin Nutr 1998; 67:452–8.
14. Armar-Klemesu MA, Wheeler EF, Brakohiapa LA, Yamamoto S. Infant feeding and growth in rural Ghana: is the use of the traditional fermented porridge a case for early supplementation? J Trop Pediatr 1991;37:111–5.
15. Zumrawi FY, Dimond H, Waterlow JC. Faltering in infant growth in Khartoum province, Sudan. Hum Nutr Clin Nutr 1987;41C:383–95.
16. Harrison GA, Brush G, Zumrawi FY. Interrelationships between growth, weaning and disease experience in Khartoum infants. Eur J Clin Nutr 1992;46:273–8.
17. Madhavapeddi R, Ramachandran P. Growth of urban breastfed infants from low socio-economic group. J Trop Pediatr 1993;39:328–31.
18. Lopéz Bravo I, Cabiol C, Arcuch S, Rivera E, Vargas S. Breast-feeding, weight gains, diarrhea, and malnutrition in the first year of life. Bull Pan Am Health Organ 1984;18:151–63.
19. Stuff JE, Garza C, Boutte C, et al. Sources of variation in milk and caloric intakes in breast-fed infants: implications for lactation study design and interpretation. Am J Clin Nutr 1986;43:361–6.
20. Hop LT, Gross R, Giay T, Sastroamidjojo S, Schultink W, Lang NT. Premature complementary feeding is associated with poorer growth of Vietnamese children. J Nutr 2000;130:2683–90.
21. Cunningham A, Jelliffe D, Jelliffe E. Breast-feeding and health in the 1980's: a global epidemiologic review. J Pediatr 1991;118: 659–66.
22. Cohen RJ, Brown KH, Canahuati J, Rivera LL, Dewey KG. Effects of age of introduction of complementary foods on infant breast milk intake, total energy intake, and growth: a randomised intervention study in Honduras. Lancet 1994;344:288–93.
23. Piwoz EG, Creed de Kanashiro H, Lopez de Romaña GL, Black RE, Brown KH. Feeding practices and growth among low-income Peruvian infants: a comparison of internationally-recommended definitions. Int J Epidemiol 1996;25:103–14.
24. Simondon KB, Gartner A, Berger J, et al. Effect of early, short-term supplementation on weight and linear growth of 4–7-mo-old infants in developing countries: a four-country randomized trial. Am J Clin Nutr 1996;64:537–45.
25. Kusin JA, Kardjati S, van Steenbergen WM, Renqvist UH. Nutritional transition during infancy in East Java, Indonesia. 2. A longitudinal study of growth in relation to the intake of breast milk and additional foods. Eur J Clin Nutr 1991;45:77–84.
26. de Onis M, Victora CG, Garza C, Frongillo EA Jr, Cole TJ for the WHO Working Group on the Growth Reference Protocol. A new international growth reference for young children. In: Dasgupta P, Hauspie R, eds. Perspectives in human growth, development and maturation. Dordrecht, Netherlands: Kluwer Academic Publishers, 2001:45–53.

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on December 18, 2016