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Risk of Being Overweight at 5 Years of Age is Associated with Weight Gain and Energy Intake during Infancy in Formula-Fed Children

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Abstract

Background: Although rapid weight gain during infancy has been associated with overweight and obese status in children and adults, no published studies have investigated the role of infant weight gain during infancy on later adiposity while controlling for dietary intake.

Objectives: To determine the relationship between weight gain (g/kg/d at 3 months intervals) and energy intake during infancy and childhood adiposity at 5 years of age.

Methods: A cohort of healthy term infants was prospectively followed from 3 to 60 months of age (Clinicaltrials.gov: NCT00616395). Anthropometrics, body composition (nuclear magnetic resonance [Echo-MRI AH]), and dietary intake (3 day food records) were assessed at 3, 6, 9, 12, 24, 36, 48 and 60 months.

Participants/Setting: Formula-fed infants (n=152) from the central Arkansas region in the United States were recruited between 2002 and 2011.

Main outcome measures: BMI-for-age Z-score, body fat (%) and energy intake (kcal).

Statistical analyses performed: Linear and logistic regression models were used while adjusting for maternal Body Mass Index (BMI), gestational age, sex, birth weight, birth length, and energy intake.

Results: Higher weight gain (g/kg/d) between 3 and 12 months of age was significantly associated with higher BMI for age Z score (BMIZ) and higher percent body fat at 5 years of age after controlling for infant sex, gestational age, birth length, birth weight, maternal BMI and energy intake. Infants who had a BMIZ >1 at 6, 9 and 12 months had greater probabilities to have a BMIZ >1 at age 5 years (adjusted odds ratio =1.9 [95% CI: 1.1 to 3.0], 2.9 [95% CI: 1.6 to 5.2] and 3.4 [95% CI: 1.8 to 6.1], respectively, P<0.02) after adjusting for the covariates. Energy intake was significantly greater by 64 kcal/d on average between birth and 12 months of age for children who were overweight at 5 years compared to their counterparts (P<0.03).

Conclusion: Higher weight gain (g/kg/d) during infancy was associated with higher BMIZ and percent body fat at 5 years of age after adjusting for important covariates such as maternal BMI and energy intake. To prevent high BMIZ later in life, infants with high weight gain and their family may benefit from early lifestyle interventions on adequate intake and feeding cues.

Keywords: Infant, Growth, Obesity, Infant formula

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Introduction

The prevalence of overweight and obesity in children remains a significant public health concern. In the United States, 42% of children between ages 2 and 5 years are overweight or obese [1-3]. Excess fat mass during infancy has been associated with impaired metabolic health during childhood and is a risk factor for adult obesity [4,5]. Because of the difficulties associated with reversing obesity once established, attempts to prevent childhood obesity and its long-term health consequences should begin very early in life [4,6,7]. Understanding the risk factors that lead to the development of obesity is important in seeking prevention strategies to tackle the obesity epidemic. Numerous studies, as well as systematic reviews and meta-analyses, have clearly demonstrated that rapid infant weight gain is associated with subsequent childhood and adulthood obesity [8-10].

Specifically, studies in diverse ethnic populations have determined that infant weight gain during the first months of life is associated with obesity later in childhood and adulthood (from age 2 to 20 years), independent of birth weight in most cases [11-26]. While studies have examined the effects of variables such as maternal Body Mass Index (BMI) and mode of infant feeding on rapid weight gain during infancy, no study to the knowledge of the authors has directly controlled for energy intake when examining the relationship between infant weight gain trajectory and subsequent obesity risk [27-32]. Given that energy intake and energy expenditure are key factors in weight gain, it would be expected that energy intake is a major driver of observed differences in weight gain during infancy. Energy intake would also be a modifiable factor that could be targeted by prevention strategies in at-risk populations. This study was set out to fill this knowledge gap by examining the relationship between weight gain during the first year of life and body composition at age 5 years in a longitudinal cohort of formula-fed infants while controlling for maternal BMI, gestational age, birth weight, birth length, sex, and energy intake during the first year of life. It was hypothesized that greater weight gain during the first year of life would lead to greater adiposity at age 5 years, and that these effects would be mainly driven by child's energy intake during the first year of life.

Materials and Methods

Participants

Participants were infants enrolled in the longitudinal cohort, the Beginnings Study (Clinicaltrials.gov: NCT00616395) and were recruited from the Central Arkansas region between ages 1 and 2 months between 2002 and 2011. Details regarding the study design and cohort specifics have been reported previously [33]. Pregnancies were reported to be uncomplicated with no medical diagnoses or medications known to affect fetal or infant growth and development. All mothers were non-smokers, who reported no alcohol use during pregnancy. Infants were term (>37 weeks), weighed between 2.7 kg (6 lbs) and 4.1 kg (9 lbs) at birth and had no abnormal medical diagnoses. Gestational age, birth weight, birth length, race, and infant sex were self-reported by the mother at enrollment. Maternal BMI was computed from self-reported pre-pregnancy weight and measured maternal height at 3 months postnatal. Only infants who were formula-fed were included in this analysis. The study was approved by the Institutional Review Board of the University of Arkansas for Medical Sciences and written consent was obtained prior to study procedures.

Infant diet

Parents, following the advice of their pediatricians, made decisions about which diet to feed their infant before enrolling in the study [33]. All formula-fed infants remained on their selected formula from age 2 to 12 months, i.e. formula-fed participants did not change feeding group during the study period. Participants were fed either cow's milk-based formulas or soy-based formulas. All participants introduced solid foods after 4 months of age.

Dietary intake

Primary caregivers were provided instruction on how to complete the three days infant food records by a trained nutritionist. Primary caregivers were instructed to record all liquids, solids, herbals, vitamins, minerals and medications consumed by the child. The records were analyzed using the Nutrition Data System for Research (University of Minnesota, Minneapolis, MN) at 3, 6, 9 and 12 months by trained nutritionists and total mean caloric intake (kcal/d) was computed for each three days period [34]. Only food records reported to be the infant's usual amounts of food by their primary caregivers were included in the analyses.

Anthropometrics

Anthropometric measures (recumbent weight and length) were obtained at each study visit (2, 3, 4, 5, 6, 9, 12, 24, 36, 48 and 60 months) using standardized methods. Briefly, infant weight was measured to the nearest 0.01 kg using a tared scale (SECA 727, SECA Corp., Ontario, CA) wearing a diaper only. Infant length was measured to the nearest 0.1 cm by using a length board (Easy Glide Bearing Infantometer, Perspective Enterprises, Portage, MI) up to age 2 years. Child height was measured to the nearest 0.1 cm using a stadiometer from age 2 to 5. BMI for age Z scores (BMIZ) were computed from the World Health Organization (WHO) growth standards according to the Centers for Disease Control and Prevention (CDC) recommendation using WHO Anthro software version 3.2.2 [35,36]. Weight gain was computed in g/kg/d at the following intervals: birth 3 months, 3 to 6 months, 6 to 9 months and 9 to 12 months.

Body composition

Body composition was assessed using dual-energy X-ray absorptiometry (DXA, Hologic QDR 4500 with discovery upgrade, Hologic Inc, Bedford, Massachusetts) at 5 years of age. Children were lying on a receiving blanket wearing only underwear to ensure consistency in DXA scan acquisition [37,38]. Scans were reviewed and all scans without movement artefact were analyzed using pediatric whole-body mode (QDR software for Windows XP, version 12.3, Hologic Inc, Bedford, Massachusetts) [39]. Total body fat mass (%) was computed by the QDR software.

Statistical analyses

BMIZ at age 5 years was used to dichotomize participants into two outcome groups (BMIZ ≤ 1 [normal weight] or >1 [overweight and obese]). The CDC defines a child as overweight if BMI percentile is greater than the 85th percentile and obese if greater than the 95th percentile which correspond to z-scores of 1.04 and 1.65, respectively [40]. Participant characteristics of the two outcome groups were summarized as means and standard deviation and compared using Wilcoxon rank-sum test for continuous variables, whereas categorical variables were summarized as counts and percentages and compared using Fisher's exact test. The relationship between body weight and body composition (BMIZ and percent body fat mass) was modeled using linear mixed models adjusted for maternal BMI, gestational age, birth weight, birth length, infant sex, type of infant formula (milk or soy formula) and energy intake during the first year of life. The model included participant level random intercepts and random slopes and was fitted via maximum likelihood estimation. An unstructured matrix was assumed for the variance-covariance structure of the random effects. From the fitted models, predicted values (fixed-portion linear prediction plus contributions based on predicted random effects) were computed and used to test the correlation between body weight gain during early infancy and body composition at 5 years of age. Unconditional logistic regression was used to compute the odds ratio (OR) and the 95% confidence interval (95% CI) for the association between BMIZ outcome (≤ 1 or >1) at age 5 years and BMIZ status (≤ 1 or >1) at age 3, 6, 9 and 12 months, while adjusting for maternal BMI, gestational age, birth weight, birth length, infant sex, type of infant formula and energy intake. Analyses were performed using the Stata statistical package version 15.0 (Stata

Table 1: Demographics of a cohort of 152 formula fed children who were normal weight or overweight by age 5 years.

BMI-for-age z-score at 5 years							
	All		≤ 1		>1		p-value
	N	%	N	%	N	%	
All	152		113	113	39	39	
Maternal Age at Delivery (Years)							0.42
Less than 27	36	24	29	81	7	19	
27 to 30	37	24	29	79	8	22	
Greater than 30	79	52	55	70	24	30	
Marital Status							0.11
Married/Cohabitate	144	95	105	73	39	27	
Single/Separated	8	5	8	100	0	0	
Mother's Education							0.08
Graduate school	42	28	26	62	16	38	
College/tech school	101	66	79	78	22	22	
High School or less	9	6	8	89	1	11	
Household Income (USD)							0.79
Greater than 60,000	9	6	8	89	1	11	
20,000 to 60,000	47	31	33	70	14	30	
Less than 20,000	91	60	68	75	23	25	
Missing[a]	5	3	4	80	1	20	
Infant Race[b]							0.81
African-American	14	9	11	79	3	21	
White	133	88	99	74	34	26	
Other	5	3	3	60	2	40	
Infant Sex							0.58
Females	81	53	62	77	19	24	
Males	71	47	51	72	20	28	
Type of Formula							0.71
Cow's milk based formula	75	49	57	76	18	24	
Soy based formula	77	51	56	73	21	27	

[a]Missing values were included in the comparison. [b]Other races included Asian and mix race

Corporation, College Station, TX) and statistical significance was set at P ≤ 0.05 [41].

Results

Of the 152 formula-fed infants who participated, 88% were White, 47% were males and all were appropriate-for-gestational age at birth (2.5 kg to 4 kg). By age 5 years, 113 children were at or below BMIZ of 1 (normal weight) and 39 children (35%, 20 males and 19 females) were above BMIZ of 1 (overweight). There were no significant differences between groups in maternal age, education, income or marital status. Groups did not differ significantly in gestational age, race, birth length, sex or type of infant formula during the first year of life (Table 1 and 2). Birth weights were higher for children who were overweight by 5 years of age (P=0.05) and BMI-for-age Z-score at birth was significantly lower in normal weight children at 5 years of age (Table 2). Maternal BMI was significantly higher for overweight children at age 5 years (P<0.01). Energy intake (kcal/d) was significantly greater by 44, 47, 74 and 89 kcal/d at 3, 6, 9 and 12 months, respectively, for children who were overweight at 5 years compared to their counterparts (P<0.03, Table 2). There were no significant differences in macronutrient ratios (carbohydrates, protein and fat) between the two groups (data not shown). BMIZ trajectories during the first year of life were significantly different for infants who were classified as normal weight *vs.* overweight at 5 years of age (Figure 1). Overweight children at 5 years of age had significantly higher BMIZ at birth and from age 6 months to age 5 years compared to normal weight children at 5 years of age. Infant sex or type of infant formula did not significantly alter BMIZ trajectories in this cohort (data not shown). Higher BMIZ at 5 years of age were significantly associated with higher infants' weight gain (g/kg/d) between 3 and 6 months, 6 and 9 months, and 9 and 12 months (Rho =0.18 to 0.34, CI: 0.015 to 0.472, P<0.05), after adjusting for infant sex, gestational age, birth length, birth weight, maternal BMI, and energy intake (Table 3). Higher body fat (%) at age 5 years was also significantly associated with higher infant weight gain (g/kg/d) between 3 and 6 months, 6 and 9 months, and 9 and 12 months (Rho =0.21 to 0.47, CI: 0.047-0.589, P<0.05), after adjusting for infant sex, gestational age, birth length, birth weight, maternal BMI, and energy intake (Table 4). Higher body fat (%) at age 5 years was significantly associated with being a female (β=3.9 to 4.6, P<0.01), and having a mother with higher BMI (β=0.3, P<0.01) at each interval during infancy after adjusting for covariates. Infants who were overweight (BMIZ >1) at 6, 9 and 12 months had greater probabilities of being

Table 2: Maternal BMI, infant birth variables and energy intake during the first year of life for children who were normal weight or overweight by age 5 years.

BMI-for-age z-Score at 5 Years					
	≤ 1		>1		p-value
	Mean	SD	Mean	SD	
Maternal Characteristics					
Body Mass Index[a] (kg/m^2)	27.6	5.7	33.3	6.6	<0.001
Infants Characteristics					
Gestational age (weeks)	39	1	38.8	0.9	0.51
Birth length (cm)	51.1	2.3	50.9	2.6	0.58
Birth weight (kg)	3.4	0.4	3.6	0.4	0.05
BMI-for-age Z-score at birth	-0.2	1.1	0.3	1.02	0.02
Energy intake[b] (kcal/d) at 3 months	646.9	121	690.4	136	0.045
Energy intake[b] (kcal/d) at 6 months	686.6	100	733.6	118	0.02
Energy intake[b] (kcal/d) at 9 months	777.6	131	851.9	130	<0.01
Energy intake[b] (kcal/d) at 12 months	916.3	187	1005.5	269	0.02

[a]Self reported pre-pregnancy weight and measured height at 3 months postnatal. [b]Obtained from 3 days food records provided by the primary caregiver and analyzed with the Nutrition Data System For Research

Table 3: Associations between weight gain during the first year of life and BMI-for-age z-score at age 5 years adjusting for infant sex, gestational age, birth length, birth weight, maternal [a]BMI and [b]Energy intake during the first year of life (N=149).

BMI[a] and Energy Intake[b] During the First Year of Life (N=149)			
	Rho	95% CI	p-value
Birth to 3 months	-0.002	0.163, 0.159	0.98
3 to 6 months	0.175	0.015, 0.327	0.033
6 to 9 months	0.337	0.186, 0.472	<0.001
9 to 12 months	0.199	0.039, 0.348	0.015

[a]Self reported pre-pregnancy weight and measured height at 3 months postnatal. [b]Energy intake obtained from 3 days food records analyzed with the Nutrition Data System for Research

Table 4: Associations between weight gain during the first year of life and percent body fat at age 5 years while adjusting for infant sex, gestational age, birth length, birth weight, maternal BMI[a] and energy intake[b] during the first year of life (N=140).

BMI[a] and Energy Intake[b] During the first Year of Life (N=140)			
	Rho	95% CI	p-value
Birth to 3 months	0.114	0.275, 0.053	0.18
3 to 6 months	0.212	0.047, 0.365	0.012
6 to 9 months	0.468	0.328, 0.589	<0.001
9 to 12 months	0.225	0.061, 0.376	0.008

[a]Self reported pre-pregnancy weight and measured height at 3 months postnatal.
[b]Energy intake obtained from 3 days food records analyzed with the Nutrition Data System for Research

Table 5: Associations between BMI-for-age z-score >1 during the first year of life and having a BMI-for-age z-score >1 at 5 years.

Age	OR	95% CI	p-value	Adjusted OR[a]	95% CI	p-value
3 months	1.5	0.9-2.3	0.09	1.3	0.8-2.2	0.36
6 months	1.7	1.1-2.5	0.01	1.8	1.1-3.0	0.01
9 months	2.3	1.5-3.7	<0.001	2.9	1.6-5.2	<0.001
12 months	2.8	1.7-4.7	<0.001	3.3	1.8-6.1	<0.001

[a]Adjusted for maternal BMI, gestational age, sex, birth weight, birth length, type of formula and energy intake during the first year of life

overweight at 5 years of age: adjusted odds ratio =1.9 (95% CI: 1.1 to 3.0), 2.9 (95% CI: 1.6 to 5.2) and 3.4 (95% CI: 1.8 to 6.1), respectively, after adjusting for maternal BMI, gestational age, sex, birth weight, birth length, type of infant formula and infants' energy intake (Table 5). The later in infancy a child was overweight, the higher the risk of being overweight at age 5 years (P<0.00).

Discussion

In this Arkansas cohort of infants and children, BMIZ at birth and between 3 and 12 months of age were significantly higher in children who were overweight at 5 years of age (BMIZ >1) compared to their counterparts (BMIZ ≤ 1). There were no significant differences between the two groups of infants with respect to maternal age, maternal education, household income, marital status, gestational age, race, birth length, sex, and type of infant formula. As expected, higher weight gain during infancy was significantly associated with higher BMIZ at 5 years of age. These findings are consistent with the current literature demonstrating that changes in weight status in infancy may influence risk of later obesity even more than weight status at birth [9-26]. There is some variation in reports examining sensitive period of development within the first year of life for later risk of obesity. Two studies reported that rapid weight gain during the first 3 to 4 months of life was strongly associated with childhood overweight at age 2 to 7 years, which reflects a slightly different critical period of development compared to the present results [23,42]. However, another study found that weight gain between 0 to 8 months was associated with increased odds of overweight and obesity at 6 to 11 years of age suggesting a somewhat longer critical time period [21]. These differences may be driven by cultural, dietary, and population genetics differences. The current study reports that greater weight gain between 3 to 12 months was significantly associated with overweight at age 5 years and that being overweight between 6 to 12 months significantly increased the odds of overweight by 5 years of age. Energy intake during infancy was a significant contributor to subsequent childhood BMIZ in this cohort, which is in agreement with previous findings that higher energy intake at 4 months of age predicted increased body weight and BMI at ages 1 to 5 years [43].

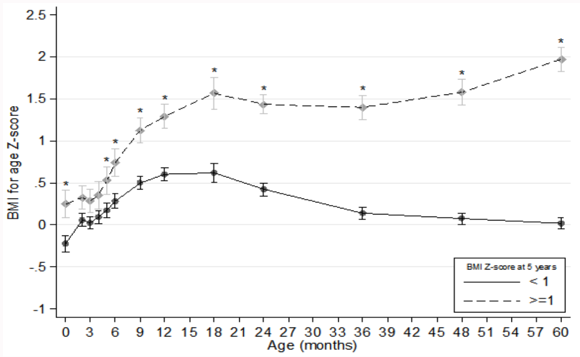

Figure 1: BMIZ trajectories in first year of life.

These findings suggest that interventions to optimize energy intake in infancy as well as interventions during gestation to decrease birth weight may be successful in achieving lower risk of overweight later in life. The associations between weight gain at age 3 to 12 months and BMIZ at 5 years of age were still significant after adjusting for infants' energy intake, maternal BMI, and other important covariates. These results suggest that other factors, such as individual differences in metabolism or energy expenditure may strongly influence the relationship between weight gain during infancy and overweight status at 5 years of age. Some studies have found that infants born to obese mothers have lower energy expenditure, although this finding has not been consistent across all studies [44-47]. Many prenatal and perinatal factors may also modulate energy expenditure during the first year of life including gestational weight gain, maternal diet, and genetic and epigenetic factors [48-50]. Most likely, a combination of these and other, yet to be identified, factors leads to differences in weight gain during infancy and ultimately to a greater risk of obesity in older children or young adults. The study also demonstrated that greater weight gain between 3 and 12 months of age was significantly associated with higher percent body fat at 5 years of age, suggesting that higher weight gain early in life leads to greater adiposity later in life. These results are in line with previous cohorts demonstrating a link between higher weight gain in infancy and greater adiposity levels at age 6 to 18 years [18,22,26,51]. There was a strong effect of sex and maternal BMI on subsequent adiposity. There was no significant sex effect in the BMIZ data, likely because BMI-Z scores are calculated using age and sex-specific adjustments. It may be important for health care providers to identify infants who are rapidly gaining weight, as these children are likely at risk for future development of obesity and might benefit from early interventions [52]. Indeed, several randomized clinical trials have demonstrated that interventions which educate parents about topics such as recognizing hunger and satiety cues, healthy eating behaviors, and introducing solid foods can reduce excessive weight gain during infancy [53-56]. These types of interventions can be implemented soon after birth and can be delivered by nurses or dietitians in an office or home setting [53-56]. The study had some limitations including: 1) a small sample size of 152 formula-fed children from mostly White (88%) families, which may limit the generalization of the presented results to other racial and ethnic groups or to breastfed infants; 2) potential bias in reporting energy intake using 3 days food record although dietary records analyzed with a systematic protocol is superior to food frequency questionnaires and 24 h recalls in this age group; 3) potential for residual and unmeasured confounding which could affect the results; 4) observational design which prohibits the analyses of causal relationships; and 5) physical activity was not assessed in the cohort. Nevertheless, the study is strengthened by: 1) the longitudinal nature of the data acquisition, 2) the use of DXA to estimate percent body fat, and 3) the use of energy intake estimates to understand its contribution to weigh gain during the first year of life [57,58].

Conclusion

In summary, weight gain during the first year of life was significantly associated with BMIZ and body fat (%) at 5 years of age, after adjusting for energy intake and other important covariates. Children with high weight gain and high energy intake during the first year of life and whose mothers' BMI are higher, may benefit from early lifestyle interventions to prevent the development of obesity. Further studies investigating the underlying mechanisms regulating energy balance in the context of higher weight gain leading to obesity later in life are needed. This could potentially include studies exploring the mechanisms underlying innate differences in weight gain, such as: Physical activity, energy expenditure, nutrient utilization and food intake, and/or the role of the gut micro biome in nutrient utilization efficiency.

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