Weight Changes Among Bottle-Fed Infants and Perspective on Obesity Prevention Beginning During Infancy

By

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Abstract

**Background:** Obesity risk in children may relate to early feeding decisions, including that of bottle vs. breastfeeding, with bottle-fed infants at higher risk for faster growth and more adiposity, but the relationship is not fully elucidated. Different size bottles are used for feeding infants, and our prior research suggests that larger bottle size is related to greater formula intake. Here we examine if the bottle size used at 2 months of age independently predicts greater change in weight and weight-for-length z-scores from 2 to 6 months of life.

**Methods:** We reviewed the literature to examine the landscape and limitations of studies that predict risk and discern reported association between bottle feeding and weight gain. We then performed a longitudinal analysis of infants enrolled in Greenlight, a cluster randomized trial to prevent childhood obesity at 4 pediatric resident clinics. Caregivers of exclusively formula-fed infants reported usual bottle size at the 2 month (baseline) visit. Bottle size was dichotomized as regular (<6 oz) or large (≥ 6 oz). We used change in weight (kg) and weight-for-length z-score (WFL-Z) from 2 and 6 months as outcomes in OLS regression models. Bottle size was the main predictor; we also controlled for study site, birthweight, sex, firstborn status, weight or WFLZ at 2 months, age in weeks, time between visits, WIC enrollment, and caregiver race/ethnicity, education, household income and size.

**Results:** 44% (n=378; 22% white, 41% black, 35% Hispanic, 2% other) of 2 month-old infants in Greenlight were exclusively formula-fed, and nearly half (46%) of exclusively formula fed babies were fed with large bottles at 2 months of age. When adjusted for covariates, infants gained 0.23 kg more over the subsequent 4 months if they used a large bottle at 2 months (95% CI: 0.06-0.39; p=0.01) and WFLZ increased by 0.34 (95% CI: 0.10-0.58; p=0.01).

**Conclusions:** We found a significant effect of using a large bottle at 2 months of age on weight gain and change in WFL z-score at 6 months of age, even when controlled for presumed covariates. Among exclusively formula fed infants, bottle size may be a modifiable risk factor for rapid infant weight gain and deserves controlled intervention study.
Overview

Due to its cardiovascular and metabolic comorbidities, obesity is a public health problem of high priority for all levels of prevention. Although research priorities have adjusted to meet the need to address obesity prevention, we still do not understand risk factors for obesity throughout the life course. Specifically, it is unknown which risk factors for obesity in childhood, which tracks to adulthood and predisposes to cardiovascular disease, diabetes, and many other comorbidities. A public health push towards breastfeeding uptake and duration as one modality to prevent obesity has gained traction with national and international agencies. However, as most infants feed by bottle at some point in the first few years of life, and many children at risk for obesity for other reasons bottle-feed exclusively, exploring risk factors, and identifying interventions to attenuate obesity risk among formula-fed and bottle-fed infants is necessary.

Literature Search Methods

In order to understand the effect of bottle feeding or formula feeding on growth and risk of overweight in infants, I searched PubMed/MEDLINE in February 2015 using the following comprehensive search strategy:

The search was limited to publications dated within the last 20 years (from January 1995 to present). Articles were eligible if they were cohort or cross-sectional studies investigating the relationship between bottle feeding/formula feeding as an exposure, and weight gain or obesity risk as an outcome. I examined titles and abstracts for criteria relevant to the study question, excluding narrative reviews, commentaries and other research that was not original. Risk of bias was not assessed systematically as most articles were small cohort studies, case-control studies or cross-sectional studies.

**Literature Search Results**

Initial results found 1216 abstracts. These titles were reviewed with broad criteria for inclusion that they were based on relevance to human medicine, leaving 104 abstracts of potential relevance to the question. At the abstract stage of review, 64 publications were excluded, exemplified by categories relating to focus on a different age group, not representing original research, (e.g. narrative reviews and commentaries) or not assessing the particular association between formula or bottle-feeding and weight gain or later obesity risk or risk factors, leaving 40 publications included for this current background question. Broadly, included studies investigated differences between primarily or exclusively breastfed compared to primarily or exclusively formula-fed (or bottle fed) infants (see Figure). By comparing these groups, most studies investigated outcomes related to overweight or obese status and other measures of adiposity in early childhood and associations between other risk factors, such as serum leptin, ghrelin, and IGF-1, protein intake, and feeding behaviors. However, there was great
heterogeneity in techniques used to measure the degree and duration of formula feeding or breastfeeding, from retrospective recall, to direct measurement of intake in experimental settings. Outcomes related to adiposity generally involved weight and height measurements, skin fold thickness, and occasionally bioimpedance or other techniques used to quantify free and total fat mass.

Patterns emerged with respect to this search. In the mid to late 1990s, much research related to content of formula, specifically nucleic acids, fatty acids (e.g. docosahexaenoic acid, or DHA), and protein and the effects of these substances on infant health and growth. Throughout this period, studies related to optimizing growth of premature infants or infants with disease effecting growth were also prominent. However, other than a few small prospective studies examining differences in growth between primarily breastfed and formula-fed infants, there is a clear lack of studies framed as prevention of disease or prevention of obese and overweight children and adults. As the prevalence of obesity began to rise and be seen in younger children, the emphasis on factors related to obesity risk with regards to infant diet and nutrition and growth patterns emerged. Larger, prospective studies including infants shortly after birth through school age years have demonstrated associations between type of milk intake and adiposity, cardiovascular risk, and other factors thought to mediate obesity risk, such as endocrine and growth factors, and parental feeding behaviors.

Overall, studies found that formula-feeding infants exhibited dose-response gradients of formula intake on weight, length, and other adiposity measures. Large, prospective
studies demonstrated significant increases in weight and adiposity measures, and also with rate of weight gain, for formula-fed infants. Studies of particular interest aimed to distinguish how risk factors may relate to the mode of feeding vs. the type of milk have led to interventions designed to intervene with regard to volume of intake or feeding behaviors. In the next section of this paper, I will focus on this relationship, among proposed mechanisms, and target a novel, modifiable risk factor for rapid weight gain and later obesity: bottle size.

Discussion
A growing body of evidence suggests that infant weight gain patterns affect risk for future weight gain and obesity and its consequent cardiovascular and metabolic comorbidities. Although few large, prospective studies are relevant to the study question, there are no individual-level randomized-controlled trials addressing the mode or substance of feeding on weight gain and obesity. Therefore, the findings are limited by the feasibility of randomizing to type of infant feeding and thus are susceptible to unmeasured confounders. The findings from the literature search are also limited by the search strategy (one database, MEDLINE), language, and exclusion of studies based on one reviewer.
B. Longitudinal Analysis of Infant Bottle Size on Weight Outcomes at 6 Months

Introduction

Understanding modifiable risk factors for obesity in early life is critical to develop effective preventive interventions for obesity and its comorbidities. Rapid infant weight gain in the first few years of life, generally defined as crossing upward percentiles (≥ 0.67 SD),\textsuperscript{90-92} is a risk factor for obesity,\textsuperscript{62,91,93-96} metabolic,\textsuperscript{97} respiratory,\textsuperscript{98} and cardiovascular disease.\textsuperscript{99-102} Although growth trajectories in infancy are determined by multiple factors, including genetic predisposition, nutrition plays a primary role. While breastfed infants exhibit more rapid weight gain and adiposity in early infancy, the rate of weight gain decreases later, and infant primarily fed formula have greater adiposity in late infancy and early childhood\textsuperscript{103,104} and greater risk of obesity later in life.\textsuperscript{105} The relationship between nutrition source and adiposity could be related to formula itself, which generally has a higher protein content,\textsuperscript{106} or to behaviors such as feeding on a schedule, which is more common in bottle-fed infants\textsuperscript{107} or to confounders such as timing of introduction of complementary foods, parental education or other socioeconomic factors.

Experimental data have shown that bottle-fed infants have less control over the volume and course of feeds, and do not assume a diurnal pattern of intake seen in breast-fed infants.\textsuperscript{108} If uniform intake remains as complementary foods are introduced, bottle-fed infants may also receive more calories per day than breastfed infants, who are better able to titrate intake to meet their needs. Some have hypothesized that the first few weeks and months of life are a critical period for the development of long-term hunger and satiety cues. Environmental influence of feeding patterns, both volume and frequency of feeds,
may alter these neuroendocrine pathways and satiety mechanisms that could influence intake and energy utilization over the life course.\textsuperscript{109-111}

Specific “environmental” components, such as the size of the bowl, plate, or glass container are known to be powerful cues that are positively associated with both portion sizes and energy intake, and are routinely utilized by the food industry to market novel products.\textsuperscript{112-114} Although much of this research has focused on adults and children, it is possible that similar environmental cues exist for feeding behaviors related to the size of the bottles used to feed infants. Nearly all parents use a bottle to feed their infant at some point during their infancy, and for many parents, particularly racial and ethnic minorities and those in under-resourced households, the bottle is the primary feeding mode for at least the first year of life. There are a wide variety of bottle sizes used and marketed for use throughout infancy, yet clinical guidance related to bottle sizes does not consistently occur. In order to determine whether environmental cues related to bottle size effect changes in infant growth, we investigated bottle size as an exposure for changes in weight and weight-for-recumbent among a diverse group of young, exclusively formula-fed infants. We hypothesized that infants whose parents were using a larger bottle at 2 months would have higher weight-for-age z scores and higher weight-for-recumbent length z scores at 6 months of age compared to infants using smaller bottles.

\textbf{Methods}

\textit{Population}
We performed an analysis of longitudinal data from the Greenlight Intervention Study, a previously described cluster randomized trial of an obesity prevention intervention delivered in clinics for children and their parents between the 2 month and 24 month well child preventive visit. Parents-infant dyads were enrolled at the 2 month well visit at 4 pediatric residency continuity clinic sites from December 2009 through June 2014. To be included in the study, infants were between 6 and 16 weeks of age at the 2 month visit, were born at ≥ 34 weeks gestation weighing > 1500 grams, and had weight-for-recumbent length ≥ 3rd percentile, based on WHO growth standards, at the 2 months visit. Infants were excluded if they had medical conditions that affected growth, such as failure to thrive. Parents were English or Spanish-speaking, ≥ 18 years of age, with adequate vision, and without severe mental or neurologic illness or plans to leave the clinic within the upcoming 2 years. Participants at the two intervention sites received a literacy and numeracy-sensitive intervention targeting obesity prevention, which was based on social cognitive theory. This low-literacy toolkit encouraged behaviors associated with healthy lifestyles and included a health-communication curriculum for the child's health care provider. The two control sites implemented an “active control” injury prevention curriculum designed by the American Academy of Pediatrics and commonly used throughout primary care clinics. The low-literacy toolkit did not specifically address the size of the bottle as a component of the intervention. We obtained written and verbal consent from parents according to the institutional review board procedures of each of the four sites.

**Measures**
Our analysis used responses from a survey of diet and physical activity at the baseline (2 month) visit in conjunction with measurements of weight and recumbent length at the 2 month and at the 6 month well child visit. The survey instrument assessed feeding behaviors, content of feeds, and other information considered of importance in obesity risk through a synthesis of relevant literature and expert opinion. Greenlight study personnel administered the instrument in person at the baseline visit. Clinic staff with enhanced training in accurate weight and length measurement recorded the infant’s weight and length in the electronic medical record at each well child visit.

**Exposure Variables**

In order to isolate a potential relationship between bottle size and weight and length changes, we included only parents who responded “formula only” to the question: “What type of milk does your child drink now?” at the 2 month visit. Our main exposure was bottle size used at this visit, which was directly verified and recorded by study personnel after an affirmative response to the question: “Do you have one of the bottles with you that you use to feed [child’s first name] formula?” In the case of the parents not having a bottle with them (2% of sample), they were asked to choose from bottles placed before them of either a 4 ounce, 6 ounce, or an 8 ounce bottle to represent the one most like the one they usually used to feed their child. We dichotomized bottle size at 6 ounces as an a priori decision based on what represents adequate nutrition for average stomach volume at that age, and from this point forward refer to “larger” bottles as those ≥ 6 ounces at the 2 month visit.
**Outcome Variables**

Our primary outcome was change in weight-for-recumbent length z score between the 2 month and the 6 month measurements. We also investigated change in weight and weight-for-age z scores. Weight and length were measured through standard clinic procedures. We calculated z scores based on the WHO sex-specific growth curves. We included covariates in our models that were available in our dataset and might confound the relationship between bottle size and growth between 2 and 6 months of age. These variables included the infant’s sex, race/ethnicity, birth weight, weight and length measures at the 2 month visit, age at the 2 month visit, and time elapsed between the 2 and 6 month visits. Additionally, we included socioeconomic characteristics including household size, household annual income, level of completed education by the primary caregiver, and whether or not the infant received assistance through WIC.

**Analysis**

We first compared the above covariates by exposure to either small or large bottles and tested the statistical significance between groups with t tests and Pearson’s chi-square tests. Next we compared unadjusted relationships between bottle size and change in weight, weight-for-age z score, and weight-for-recumbent length z score between 2 and 6 months with linear regression. Our final step examined three models of adjusted linear regression with weight change, weight-for-age z score change, and weight-for-recumbent length z score change as outcomes, and infant sex, race/ethnicity, birth weight, and the appropriate 2 month measure depending on the model, in addition to other socioeconomic characteristics as covariates. All statistical tests were run using Stata version 13.
Results

A total of 1805 parent-infant dyads were assessed for eligibility for enrollment in the Greenlight study. Of these, 632 potential participants were excluded, most commonly when the parent had plans to move or did not plan to attend all visits through 2 years, leaving 1173 eligible. Approximately three-quarters (73.7%, or 865) of eligible participants enrolled, with 386 (45%) of parents feeding only formula at the baseline (2 month) visit, which represents our sample for analysis. Most infants in our sample were of racial/ethnic minority groups (76%), from households earning less than the federal poverty guidelines for a family of four (62%), and with parents having less than or equal to a high school diploma (63%). Additional socioeconomic characteristics of our sample are shown in Table 1. As this is a generally under-resourced population, most (86%) received assistance from WIC for their infants, and in only 39% of families was the infant the only child. Most primary caregivers were mothers (95%), 77% preferred to speak in English, nearly half (46%) were unemployed and not looking for work at the time of enrollment, 18% were looking for work, and 36% were working either part-time or full-time.

Mean (SD) birth weight and weight at the 2 month visit were 3.2 kg (0.6) and 5.3 kg (0.8), respectively. Just over half of formula-fed infants were female (53%), and mean (SD) age at the 2 month visit was 9 weeks (1.8). This sample had slightly below average birth weight-for-recumbent length, calculated as -0.52 (SD 1.1), increasing to 0.27 (SD 1.1) at the 2 month visit. Weight-for-age z score at the 2 month visit was -0.31 (SD 0.96).
The time between the baseline (2 month) visit and the 6 month visit ranged from 12 weeks to 30 weeks, with a mean (SD) time of 19.5 weeks (3.1), and over this period of time, infants gained an average of 2.74 kg (SD 0.7), with weight-for-age z score change of 0.44 units (SD 0.7) but no overall changes in weigh-for-recumbent length z score change (0.00, SD 1.1).

Parents used bottles that were 2 ounces in size up to 10 ounces in size. When dichotomized at 6 ounces, 55% of parents reported using a “smaller” bottle (< 6 ounces) and 45% used a “larger” bottle ≥ 6 ounces (Table 1). The only statistically significant difference between socioeconomic characteristics and bottle size was within the overall category of race/ethnicity (p=0.012). When this association was examined pairwise, Hispanic parents were half as likely to use a small bottle (OR=0.57, 95%CI: 0.33-0.99).

We found statistically significant relationships between bottle size and age at the 2 month visit, weight of the infant at the 2 month visit, and the infant’s sex. Infants using larger bottles were more likely to be male (OR=1.54, 95% CI: 1.02-2.32) and older, with 14% higher odds of larger bottle use with each week older (OR=1.15, 95% CI: 1.03-1.29). Infants weighing more at the 2 month visit had higher odds of using a larger bottle (OR=1.56, 95%CI: 1.19-2.05), yet there were no significant differences between parents using larger bottles and the infant’s birth weight, weight-for-length z score at birth or at 2 months. Furthermore, there were no significant relationships between bottle size and times between the 2 and 6 month visit or whether or not the infant was an only child.
Using unadjusted linear regression, we found that use of a larger bottle at 2 months predicted 0.16 kg more weight gain (95% CI: 0.01-0.32, p=0.043), and an additional 0.18 units weight-for-age z score change (95% CI: 0.01-0.34, p=0.034) between the 2 and 6 month visits. Infants using larger bottles also gained an additional 0.26 units of weight-for-length z score over the period (95% CI: 0.00-0.52, p=0.05). When adjusting for the appropriate growth parameter at 2 months, birth weight, time between visits, Greenlight study site, and other socioeconomic covariates, the relationships between bottle size and weight change, weight-for-age z score change, and weight-for-recumbent length z score change remained significant (Table 2). Weight change, and weight-for-age z score change was 0.24 (95% CI: 0.08-0.40) and 0.27 (95% CI: 0.11-0.44), respectively. Weight-for-length z score change, a common surrogate for adiposity, changed by 0.36 units more in infants using a larger bottle (95% CI: 0.13-0.60, p=0.003).

**Discussion**

In a large, multisite sample of diverse, low-income, formula-fed infants, we found that use of a large bottle at 2 months predicted significant changes in weight and weight-for-length z score change, even when adjusting for confounding factors. Z score changes of this magnitude, and over a relatively short period of time, may reflect a significant environmental influence of bottle size on volumes of formula given to infants, and trigger parents to overfeed their infant. Despite unclear evidence regarding the causation of rapid weight gain, upward percentile crossing (increasing by $\geq 0.67$ SD, or z score) during infancy and early childhood appears to increase later obesity risk in a stepwise fashion. Druet analyzed individual data from 10 cohort studies, finding that infants who crossed
multiple percentiles (≥ 1.33 SD) in the first year of life had nearly 4 times the odds of childhood obesity, and that change in standard deviation score (SDS, or z score) was a more powerful predictor than birth weight z score, maternal BMI, or gender. Although the weight and z score changes we found do not represent crossing a full percentile, the influence of bottle size can have a demonstrable effect on growth rate in the relatively short period of time between 2 and 6 months of life among infants fed formula exclusively. Others studying formula-fed infants have found that earlier periods, including within days of birth, may be critical periods for long-term outcomes. Stettler and colleagues studied healthy infants who exclusively fed formula since birth and found that each additional 100 grams gained in the first week of life was associated with overweight status 20 to 32 years later (OR 1.28, 95% CI: 1.08-1.52).\(^{89}\)

It is possible that risk related to formula-feeding infants is related to the mode of feeding and not the substance. Li and colleagues followed infants for one year and found that infants categorized as fed “human milk by bottle only” and “nonhuman milk by bottle only” gained more weight than breastfed infants.\(^{82}\) More recently, Li and colleagues, using 6 year follow up data from the Infant Feeding Practices Study II found that parents more frequently emptying the bottle were also more likely to practice controlling feeding behaviors and encourage the child to finish all the food on the plate.\(^{117}\) These results suggest that behaviors related to bottle feeding may have a more important role on weight gain than the substance of milk itself, and that behaviors specific to bottle-emptying might lead infants to be less responsive to satiety mechanisms. Equally, this relationship might also be explained by consistent parent feeding behaviors from infancy through
childhood, and measuring these behaviors with validated instruments could be valuable. Kavanagh randomized formula-feeding infants to an educational intervention emphasizing responsiveness to satiety cues, discouraging regular bottle-emptying, and limiting initial volumes of formula offered to no more than 6 ounces per feed. At least 2 months after the intervention, bottle-emptying behaviors increased and the intervention group had greater weight and length gain, contrary to the expected outcome. However, less than 5% of the study population at enrollment (around 2 months) used bottles containing more than 6 ounces of formula.

Interventions to reduce risk among formula fed infants have also focused on the content of formula, particularly protein content, demonstrating that infant length does not differ, but weight-for-age and weight-for-length gains are greater among groups of infants consuming a higher protein concentration. In a multicenter European study, Koletzko found that at 24 months, the group randomized to higher protein content formula had a weight-for-length z score 0.2 units higher than infants consuming formula with a lower protein content. The lower protein group had weight-for-length z scores and BMI z scores that did not differ from a group of breastfed infants followed along with the study.

Intervening to encourage healthy behaviors is a common component of obesity prevention and intervention trials, yet we have failed to identify an effective intervention to prevent obesity. However, utilizing the power of environmental cues, such as bottle
size, could provide a simple intervention that is not cognitively challenging or burdensome to carry out, and similar interventions are being studied in children.\textsuperscript{120}

\textbf{Limitations}

Our study was limited by not directly measuring intake, bottle size, or bottle-emptying behaviors over time. Families are likely using more than one bottle size, although asking parents to demonstrate the bottle used at the 2 month visit is likely to provide a reproducible, feasible way of assessing patterns of intake in the clinical setting. We were not able to follow infants from birth to 2 months, and used birth data from the health record. The period between birth and 2 months may be even more critical for intervention, although encouraging establishment of breastfeeding during this time should be of highest priority. Measurement of length during this time of infancy is especially difficult, and there is no standard, reliable measure of adiposity that clearly predicts obesity risk and can be easily measured in mobile infants, so we used both weight-for-age and weight-for-length changes to accommodate this uncertainty. Finally, the clinical relevance of the changes we found remains unclear, and should be studied in the context of known and posited risk factors for obesity that can be detected and modified in infancy.

Regardless of whether breast feeding provides a demonstrable effect on obesity risk reduction, it is certainly top priority to promote exclusive breastfeeding for as long as is mutually acceptable to mother and infant, and to decrease socioeconomic disparities in breastfeeding exclusivity and length. Our study population resembles that of other
diverse, low-income populations, as it is already at higher risk for obesity and associated morbidities, and is engaging in behaviors known to increase risk for obesity, including formula-feeding. Addressing risk during infancy may eliminate some of these disparities, yet by 2 months, the feeding mode has been established. We should nonetheless investigate modifiable factors related to obesity risk among bottle-fed infants, whether they are regularly fed by bottle or intermittently fed by bottle. Designing patient-centered, culturally appropriate, and health literacy- and numeracy-sensitive interventions in the first years of life depends on accurately and reliably identifying these factors, and is a research priority.

**Public Health Implications**

Pediatric visits to the primary clinician and public health agencies in the first year of life typically focus on maintaining adequate weight gain and nutrition and emphasizing injury prevention. Since widespread public health efforts to improve nutrition in infants and children at the turn of the century, clinicians have continued to focus on identifying and treating “failure to thrive” and generally not assessing risk based on rapid growth or weight-for-length above the highest normative percentiles. While this focus has not typically sought to address modifiable risk factors for obesity or other diseases, breastfeeding has been increasingly encouraged. In the setting of exclusive breastfeeding, weight gain and nutrition are inherently controlled by the mother-infant dyad (flexible schedule and volume of feeding, among other factors). Although stomach size has been documented and estimated for many years, evidence-based guidance about feeding volumes and schedules for infants who are bottle-fed has lagged behind other types of
guidance. Particularly among a low-income, under-resourced populations, a variety of bottle sizes are used, and many families use a size of bottle that may be inappropriate for their infant’s stomach size, if fed in their entirety or if even half of the bottle is prepared and finished. This potential for overfeeding is matched with a social norm that equates a “chubby” baby with health, both among clinicians and caregivers.

It is important to know that restricting intake is not the same as providing adequate environmental cues for food intake. The distinction between paternalism and providing a healthy environment is at times subtle. For example, an interpretation of bottle size changes that concludes “parents should know how much to feed and therefore we should prevent them from overfeeding” is inappropriate. Separately, but perhaps a delicate distinction, is the idea that all of us are influenced implicitly from environmental influences to some degree. Acknowledging this distinction and the universal effect that environmental influences have on our decision-making will allow forward progress with prevention efforts. In short, the need to provide guidance and appropriate environmental cues is not limited to a subset of the population with limited means of making appropriate judgments about food intake, but comes from a need to address cognitive distortions shared by all of us. The food industry has harnessed the power of influences of container size for years, and it’s time to appropriately study and leverage similar ideas for obesity prevention. As a public health intervention, reducing bottle size may provide benefits to broad populations who are affected and use bottles at least intermittently. Finding ways to study and promote healthy weight gain in the first year of life will reap benefits not only
for those at highest risk for obesity, cardiovascular and metabolic disease, and will push forward prevention efforts that address all aspects of risk across the life course.

References

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Table 1. Characteristics of Sample Population

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) or %</th>
<th>Small Bottle (n=208, 55%)</th>
<th>Large Bottle (n=171, 45%)</th>
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<tbody>
<tr>
<td>N=379</td>
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<tr>
<td>Race/Ethnicity*</td>
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</tr>
<tr>
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<tr>
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<tr>
<td>Household income</td>
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<tr>
<td>HS graduate</td>
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<td>College graduate</td>
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<tr>
<td>WIC enrollment</td>
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<td>85</td>
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<tr>
<td>Age at 2 mos (weeks)</td>
<td>9.3 (1.8)</td>
<td>9.1 (1.8)</td>
<td>9.6 (1.8)</td>
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<td>Female</td>
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<td>3.2 (0.5)</td>
<td>3.3 (0.6)</td>
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<td>WFLz at birth</td>
<td>-0.52 (1.1)</td>
<td>-0.6 (1.2)</td>
<td>-0.5 (1.1)</td>
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<td>Weight 2 mo (kg)</td>
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<td>5.1 (0.7)</td>
<td>5.4 (0.8)</td>
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<td>WFAz at 2 mos</td>
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<td>-0.19 (0.99)</td>
<td>-0.38 (0.94)</td>
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<td>WFLz at 2 mos</td>
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<td>0.19 (1.1)</td>
<td>0.36 (1.2)</td>
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<tr>
<td>Weeks between 2 and 6 month visits</td>
<td>19.5 (3.1)</td>
<td>19.7 (3.0)</td>
<td>19.3 (3.2)</td>
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<td>Infant is only child</td>
<td>39</td>
<td>38</td>
<td>41</td>
</tr>
</tbody>
</table>
### Table 2. Bottle Size Predicts Significant Changes in Weight and Weight-For-Length

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight change (kg)</td>
<td>0.16</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 0.01-0.32)</td>
<td>(95% CI: 0.08-0.40)*</td>
</tr>
<tr>
<td>Weight-for-age z-score change</td>
<td>0.18</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 0.01-0.33)</td>
<td>(95% CI: 0.11-0.44)*</td>
</tr>
<tr>
<td>Weight-for- length z-score change</td>
<td>0.26</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 0.00-0.52)</td>
<td>(95% CI: 0.13-0.60)*</td>
</tr>
</tbody>
</table>

*p<0.05  
**Adjusted for sex, age, race, growth parameters at 2 months, site, education, income, household size, time between 2-6 months
Figure. Flow for Study Inclusion

1216 articles retrieved from MEDLINE with search criteria

104 studies included for full-text review

40 studies included after full-text review

1,112 studies excluded after title/abstract review

64 studies excluded after full-text review