Weight Gain in the First Week of Life and Overweight in Adulthood

A Cohort Study of European American Subjects Fed Infant Formula

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Background—Successful prevention of obesity and related cardiovascular risk factors requires a clear understanding of its determinants over the life course. Rapid infancy weight gain is associated with childhood obesity, whereas low infancy weight is associated with coronary heart disease. Our aim was to identify during which periods in infancy weight gain is associated with adult obesity.

Methods and Results—A cohort of European American formula-fed subjects, measured on 7 occasions during infancy as part of several infant formula studies, were contacted at age 20 to 32 years, when they reported usual adult weight and height. A life-course plot was used to identify critical periods of weight gain associated with adulthood overweight (body mass index $\geq$25 kg/m^2). These associations were tested with logistic regressions. Data were available for 653 subjects (72% of eligible subjects). Approximately 32% of them were overweight adults. The period between birth and age 8 days was identified as potentially critical. After adjustment for important confounding factors, weight gain during the first week of life was associated with adulthood overweight status (OR for each 100-g increase 1.28, 95% CI 1.08 to 1.52), as was weight gain during the first 112 days of life (OR 1.04, 95% CI 1.01 to 1.08). Similar results were obtained after standardization with z scores from a reference population.

Conclusions—In formula-fed infants, weight gain during the first week of life may be a critical determinant for the development of obesity several decades later. These results contribute to the understanding of chronic disease programming and suggest new approaches to obesity prevention. **(*Circulation*. 2005;111:1897-1903.)**

Key Words: risk factors ■ infant formula ■ obesity ■ follow-up studies ■ pediatrics

The prevalence of obesity is increasing in the United States and globally among adults and children.[1–5] Because obesity is a major risk factor for cardiovascular diseases, evidence-based strategies to prevent obesity are increasingly urgent priorities to prevent cardiovascular diseases. Owing to renewed interest in a life-course approach to chronic disease epidemiology and prevention,[6] the potential for interventions during critical periods has been explored in several observational studies.[7,8] In particular, our group and others have shown that a rapid weight gain in infancy is associated with the development of childhood obesity in populations of European, African, and Asian ancestry.[9–16] We have also shown that rapid weight gain in the first 4 months of life is associated with obesity in a sample of young black adults,[17] whereas others have shown a similar association in young Swiss adults.[18] It is unclear, however, whether this association remains present later in adulthood and which specific period in infancy is critical for the long-term risk of obesity.

Another body of research has addressed the association of early growth patterns with cardiovascular risk factors and diseases. Although low birth weight has been associated consistently with elevated blood pressure and coronary heart disease,[19–22] the association of infancy weight gain with cardiovascular risk factors and diseases remains controversial. Coronary heart disease has been associated with low weight during infancy in observational studies,[23,24] whereas experimental studies in human and animals have described increased cardiovascular risk factors with rapid weight gain during early infancy.[25–29] Because infancy weight gain is a potential target for preventive interventions, it is critical to understand better the association between infancy growth patterns and the development of cardiovascular risk factors, including obesity.

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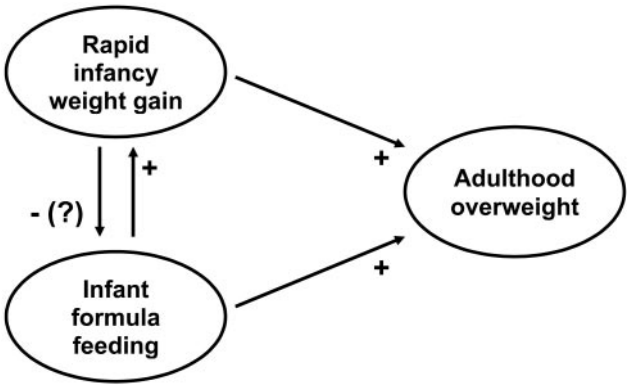

Figure 1. Conceptual model for hypothesized associations of infancy weight gain and feeding mode with adulthood overweight.

Most observational studies describing the association between infancy weight gain and later obesity did not include repeated measurements during infancy and therefore could not identify a narrower critical period. Most studies had limited information on the mode of infant feeding, thus limiting the interpretation of the association between rapid weight gain in infancy and later obesity. The association of infancy weight gain with later obesity may be, at least in part, on the pathway and explained by the association between infancy feeding mode and the development of obesity, as illustrated in Figure 1. Formula feeding is associated with a more rapid weight gain in early infancy[30,31] and with an increased risk for obesity in childhood and adolescence.[32,33] On the other hand, breastfed infants with a slow weight gain may be more likely to receive formula supplements or to be shifted to formula because of fear of undernutrition. It is also possible that feeding mode modifies the association between infancy weight gain and later obesity (interaction). Because breast milk production is stimulated by the infant's suckling, it is unlikely that a rapid weight gain in exclusively breastfed infants is due to overfeeding, although this is possible in formula-fed infants and could lead to an increased risk for later obesity. Therefore, adjustment for feeding mode, for example, by restricting a study to formula-fed infants, is important to understand the association of infancy weight gain with later obesity. The aims of the present study, then, were to define which narrow period during infancy is critical for the development of adulthood overweight status and to test the hypothesis that weight gain in infancy is associated with adulthood overweight status in a sample restricted to subjects of European descent who were exclusively formula-fed.

Methods

This is a secondary analysis of data from a cohort of subjects who, as infants, participated in a number of feeding studies, both published[34,35] and unpublished, that involved a number of different cow milk–based and soy-based formulas and who later participated in a follow-up study designed to investigate the effect of these formulas on pubertal development and reproductive history.[36] Participants in the original cohort study were healthy infants born between 1965 and 1978 in the region of Iowa City, Iowa, whose mothers elected not to breastfeed. The source population was all infants born at or above 2500 g living in and around Iowa City at the time of the study. Recruitment was by word of mouth or by visits to maternity wards in the area, and no attempt was made to document the response rate for recruitment of the original cohort. With few exceptions, all subjects were of European descent, which reflects the racial composition of the area at that time. The subjects were enrolled at age 8 days and followed up to age 112 days as part of several nonrandomized studies of infant feeding and growth. One of the inclusion criteria for the original study was no breastfeeding before enrollment, not even for 1 day. Therefore, none of the infants were breastfed before or during the study. Depending on the study taking place at the time of their birth, they were assigned to the infant formula under study at that time. Although the subjects were not strictly randomized to soy-based or cow milk–based formulas, they were assigned the formula in use at the research unit within 2 days of the time of their enrollment into the study (age 8 days), without taking into account the infant's characteristics or the parents' choice. Once assigned to a formula, the same formula was fed during the entire study period. No complementary food was allowed before 28 days of life, but, at the parents' discretion, selected complementary foods were allowed afterward, although not encouraged: after 28 days of life, oatmeal with bananas and applesauce; after 56 days of life, pears; and after 84 days of life, applesauce or bananas.[34] Some parents introduced other complementary foods not included in the protocol. Because intake of complementary foods was generally small and not completely available, this variable was not included in the analyses. The infants' weights were measured at age 8, 14, 28, 42, 56, 84, and 112 days as described previously.[37] Birth weight was reported by the mother at enrollment.

Subjects eligible for the adult follow-up study[36] were those who received only soy-based or cow milk–based formula, completed the 112 days of the infant study, were not adopted, were not from foreign countries, were not disabled, and were still alive in 1999. A national search was conducted to locate the 952 original cohort subjects using contact information from the original study and public records. A lengthy telephone questionnaire was administered by trained interviewers in 1999 to 2000 to assess pubertal and reproductive history,[36] as well as usual weight and height. Other variables of interest assessed by telephone interview included age at interview, parental weight category, and subject income category.

To adjust weight during infancy for physiological growth and gender differences, the weight-for-age z score (WAZ) in SD units was calculated by the LMS method[38] at each measurement point in infancy with a reference population of US children.[39] The LMS method uses 3 parameters (L for the power in the Box-Cox transformation, M for the median, and S for the generalized coefficient of variation) to determine an age- and gender-specific z-score value for a subject's weight.[38] This method is used by the Centers for Disease Control and Prevention (CDC) to generate z scores based on US population data.[39] Because LMS parameters are only available at 1-month increments, values were generated for age 8, 14, 28, 42, 56, 84, and 112 days assuming a linear relation of the LMS parameters between each month point. Absolute weight gains from birth to 8 days and birth to 112 days of life were calculated as the absolute difference between the 2 weights. Change in z score was defined as the difference in WAZ between birth and age 8 days and to age 112 days, respectively. Body mass index (BMI) in adulthood was calculated as self-reported usual weight in kilograms divided by self-reported adult height in meters squared. The usual definition of overweight is a BMI $\geq$25 kg/m^2 but $<$30 kg/m^2. To simplify the nomenclature, for the present study, we defined subjects as overweight if they had a BMI $\geq$25 kg/m^2 and as obese if they had a BMI $\geq$30 kg/m^2. According to this definition, all obese subjects were also overweight. The subjects' parents' weight status was reported by the subject during the interview and classified as overweight if the parent was described as somewhat or extremely overweight and nonoverweight if the parent was described as slim or average weight. The main exposure (absolute weight gain and change in z score from birth to age 8 days and birth to age 112 days), the main outcome (adult overweight status), and possible confounding variables (gender, type of infant formula used, age at interview, maternal and paternal

TABLE 1. Characteristics of Subjects in Infancy and Adulthood (as previously reported[36]) and of Their Parents

	Data Available, n	Median or Proportion	2.5 to 97.5 Percentile
Subjects in infancy			
Gender, % female	653	47.6	NA
Formula type, % soy-based formula	653	35.2	NA
Birth weight, kg	653	3.465	2.650 to 4.385
Weight at age 8 days, kg	653	3.670	2.872 to 4.607
Weight at age 112 days, kg	653	6.555	5.367 to 8.193
Absolute weight gain from birth to 8 days, kg	653	0.205	0.009 to 0.432
Absolute weight gain from birth to 112 days, kg	653	3.085	1.965 to 4.515
WAZ at birth, SD	653	0.00	−1.46 to 1.90
WAZ at age 8 days, SD	653	−0.14	−1.52 to 1.58
WAZ at age 112 days, SD	653	0.37	−1.12 to 2.08
Change in WAZ from birth to 8 days, SD	653	−0.13	−0.57 to 0.28
Change in WAZ from birth to 112 days, SD	653	0.32	−1.30 to 1.91
Subjects in adulthood			
Age, y	653	26	20 to 32
BMI, kg/m^2	653	23.2	18.0 to 32.9
Overweight (BMI ≥25 kg/m^2), %	653	32.3	NA
Obese (BMI ≥30 kg/m^2), %	653	5.7	NA
Subjects' parents			
Overweight mother, %	648	38.1	NA
Overweight father, %	632	35.1	NA

weight status, and subject's income) were explored graphically, tested for normality, and described by use of medians, percentiles, and proportions as appropriate. Subjects with complete data were compared with other subjects by χ^2 or t test as appropriate. To assess which, if any, period of weight gain in early infancy was associated with adulthood weight status, a life-course plot was constructed with adulthood overweight status as the outcome. As described in detail by Cole,[40] this method uses a logistic regression of the outcome (here, adulthood overweight status) with WAZ at each time point during growth as independent variables, adjusted for each other and for important confounding variables selected a priori on the basis of the existing literature. The β-coefficients are then plotted against time to visually assess which period of change in WAZ (slope of the life-course plot) corresponds to a sensitive or critical period for the development of the outcome. The association of weight gain during the sensitive periods and the possible confounding variables with adulthood overweight status was tested by simple logistic regression or χ^2 test as appropriate. Possible interactions of gender or formula type in the association between infancy weight gain and adulthood weight status were tested with an interaction factor in the logistic model. To test the association of infancy weight gain with adulthood weight status, while adjusting for confounding factors selected a priori on the basis of the existing literature, a multiple logistic regression model was used. Stata 7.0 was used for all statistical analyses.[41] All significance tests were 2-sided, and a probability value <0.05 was considered significant. This study was approved by the Institutional Review Board of The Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine, and the subjects gave informed consent.

Results

As reported previously,[36] among the 952 subjects of the original cohort, 904 were eligible for the adult follow-up study, whereas the others were ineligible because they received both soy- and cow milk–based formula (n=26), were deceased (n=10), were from countries other than the United States (n=7), were disabled (n=3), or were adopted (n=2). Among the 904 eligible subjects, 811 were interviewed, 51 were not located, and 42 refused to participate. Of the 811 subjects interviewed, 653 had complete data on infant growth and adult weight status. These 653 subjects (72% of the eligible subjects) constitute the sample studied in the present analysis (Table 1) and were not different at baseline from the subjects of the original cohort who were not analyzed for gender distribution ($P=0.7$), formula assignment ($P=0.8$), or birth weight ($P=0.7$). Most variables were not normally distributed and are consequently summarized with medians and percentiles. The prevalence of obesity was low in this sample compared with the general population of adults of the same age group and race,[1,5] with only 37 subjects (5.7%) reporting a usual weight and height that corresponded to obesity (BMI ≥30 kg/m^2). Although analyses that used obesity as an outcome were of interest, the small number of obese subjects did not allow for meaningful analyses. Therefore, all further analyses are reported with overweight status (BMI ≥25 kg/m^2, 32.3% of subjects) as outcome.

The β-coefficients of the adjusted association of WAZ at each infancy measurement for adulthood overweight status are presented with the life-course plot method (Figure 2).[40] The use of this plot helps identify graphically which period of weight gain may be sensitive or critical for the development of the outcome. On the basis of this figure, we chose the period between birth and age 8 days for analysis. The period

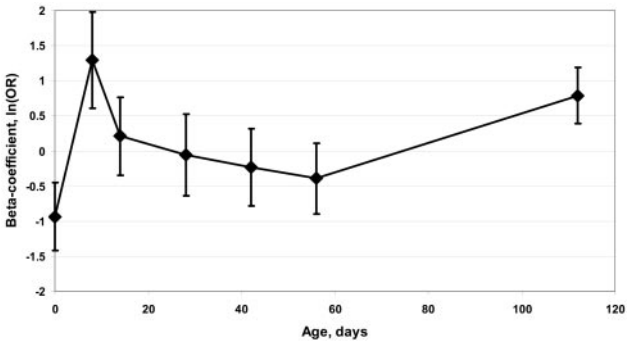

Figure 2. Life-course plot of β-coefficients (error bars representing SE) of logistic regression for adulthood overweight status (BMI $\geq$25 kg/m^2) as dependent variable and WAZ at different ages in infancy as independent variables, adjusted for each other and for gender, type of infant formula, parental weight status, and subject age and income at time of interview.

between birth and age 112 days was also chosen to compare the results of the present study to the results of other studies.[10,17] As expected, weight gain during the first 8 days of life was correlated with weight gain in the first 112 days of life, both when expressed in absolute weight gain (correlation coefficient 0.32, $P<0.001$) or in changes in z scores (correlation coefficient 0.41, $P<0.001$). Therefore, all models included only 1 period, with no attempt to adjust for the other period. The unadjusted associations of adulthood overweight status with absolute weight gain during the first 8 and 112 days of life and change in z score during the first 8 and 112 days of life, as well as the association of possible confounding variables, are presented in Table 2. The OR values cannot be compared with each other because the units of the exposure variables are different. In these unadjusted analyses, absolute weight gains during the first 8 days (OR 1.20, 95% CI 1.03 to 1.41) and the first 112 days of life (OR 1.06, 95% CI 1.04 to 1.09) were both significantly associated with adulthood overweight status, but these associations were not present when changes in z score were used (OR 0.90, 95% CI 0.41 to 1.98 and OR 1.03, 95% CI 0.84 to 1.27, respectively). No interaction with gender or formula type was detected in the association between infancy weight gain and adulthood overweight status. Table 3 reports the association of absolute weight gain or change in z score during the first 8 days and the first 112 days of life adjusted for important confounding variables selected a priori. Again, the ORs cannot be compared with each other. For consistency and ease of interpretation, absolute weight gain and birth weight are expressed in 100-g units in the absolute weight gain models, whereas changes in z score and birth weight z score are expressed in SD in the change in z score models. The adjusted analyses confirm an independent association of absolute weight gain during the first 8 days (OR 1.28, 95% CI 1.08 to 1.52) or the first 112 days of life (OR 1.04, 95% CI 1.01 to 1.08) with adulthood overweight status. Additionally, adjustment for important confounding variables uncovered existing associations of changes in z scores in the first 8 days (OR 3.62, 95% CI 1.43 to 9.18) and the first 112 days of life (OR 1.41, 95% CI 1.09 to 1.82) with adult overweight that were masked in the unadjusted analyses. Because the slope of the life-course plot between 8 and 14 days of life was also steep, post hoc analyses were performed with this interval, adjusted for weight (or weight z score as appropriate) at age 8 days and the same confounding factors as in the primary analysis. These analyses did not show statistically significant associations between adult overweight and absolute weight gain or changes in z scores during this period. Adjustment for weight at birth instead of at age 8 days yielded similar results.

Discussion

The main finding of the present study was that weight gain during the first week of life in healthy, European American, formula-fed infants was associated with overweight status 2 to 3 decades later. This finding is important, not so much to predict which infants are at risk for becoming overweight adults, but more to understand the importance of the human physiology of programming during short early-life periods on the development of chronic disease over the life course. These results also point to new potential targets for obesity prevention. The association of absolute weight gain in the

TABLE 2. Unadjusted Association of Absolute Weight Gain During Infancy, Change in WAZ During Infancy, and Potential Confounding Variables With Overweight Status in Adulthood (BMI $\geq$25 kg/m^2)

	OR	95% CI	*P*
Absolute weight gain from birth to 8 days, 100 g	1.20	1.03 to 1.41	0.02
Absolute weight gain from birth to 112 days, 100 g	1.06	1.04 to 1.09	<0.001
Change in WAZ from birth to 8 days, SD	0.90	0.41 to 1.98	0.8
Change in WAZ from birth to 112 days, SD	1.03	0.84 to 1.27	0.8
Birth weight, kg	2.63	1.77 to 3.90	<0.001
WAZ at birth, SD	1.50	1.22 to 1.83	<0.001
Female gender	0.33	0.23 to 0.47	<0.001
Soy-based formula	1.19	0.85 to 1.67	0.3
Overweight mother, %	1.72	1.23 to 2.40	0.001
Overweight father, %	1.58	1.13 to 2.21	0.008
Subject age in adulthood, y	1.05	1.01 to 1.10	0.03
Increasing subject income categories	1.02	0.93 to 1.11	0.7

TABLE 3. Adjusted* Association Between Absolute Weight Gain During Infancy, Change in WAZ in Infancy, and Potential Confounding Variables With Adulthood Overweight Status (BMI ≥25 kg/m²)

	From Birth to Age 8 Days						From Birth to Age 112 Days					
	Absolute Weight Gain, 100 g			Change in *z* Score, SD			Absolute Weight Gain, 100 g			Change in *z* Score, SD		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Infant absolute weight gain, 100 g	1.28	1.08 to 1.52	0.005	†	†	†	1.04	1.01 to 1.08	0.006	†	†	†
Infant change in *z* score, SD	†	†	†	3.62	1.43 to 9.18	0.007	†	†	†	1.41	1.09 to 1.82	0.009
Birth weight, 100g	1.08	1.04 to 1.13	<0.001	†	†	†	1.09	1.04 to 1.13	<0.001	†	†	†
Birth weight *z* score, SD	†	†	†	1.61	1.28 to 2.03	<0.001	†	†	†	1.71	1.33 to 2.21	<0.001
Female gender	0.38	0.26 to 0.55	<0.001	0.30	0.21 to 0.44	<0.001	0.45	0.30 to 0.67	<0.001	0.33	0.23 to 0.47	<0.001
Soy-based formula	1.47	1.01 to 2.13	0.046	1.46	1.00 to 2.12	0.049	1.37	0.95 to 1.98	0.1	1.37	0.95 to 1.99	0.09
Overweight mother	1.72	1.19 to 2.49	0.004	1.72	1.19 to 2.49	0.004	1.67	1.16 to 2.42	0.006	1.68	1.16 to 2.42	0.006
Overweight father	1.32	0.91 to 1.90	0.14	1.32	0.91 to 1.90	0.14	1.37	0.95 to 1.97	0.09	1.37	0.95 to 1.97	0.09
Subject age in adulthood, y	1.07	1.01 to 1.13	0.02	1.07	1.01 to 1.13	0.03	1.05	1.00 to 1.11	0.07	1.05	1.00 to 1.11	0.07
Increasing subject income categories	1.01	0.91 to 1.12	0.9	1.01	0.91 to 1.12	0.9	1.01	0.92–1.13	0.8	1.02	0.92–1.13	0.8

*Adjusted simultaneously for all variables included in each model.

†Not included in this model. For consistency and ease of interpretation, absolute weight gain and birth weight are expressed in 100-g units in the absolute weight gain models, whereas change in *z* score and birth weight *z* score are expressed in SD in the change in *z* score models.

first week of life in formula-fed infants with adulthood overweight status was clinically significant. After adjustment for important confounding factors, each 100-g increase in absolute weight gain during this period was associated with a 28% increase in the risk of becoming an overweight adult (95% CI 8% to 52%). Because the weight gain during the first week of life ranged in this sample from 0 to 400 g, a 100-g difference is within the range of normal weight gain. From this observational study, it is unclear whether this association was causal, due to unmeasured confounding factors, or whether both weight gain in the first week of life and adult overweight were determined by underlying factors, such as genetic predisposition to obesity expressed early in life. However, an intervention study of premature infants randomized for ≈4 weeks to usual or enriched nutrition that resulted in increased weight gain suggests that the impact of growth patterns in early postnatal life on the development of cardiovascular risk factors, such as high blood pressure, insulin resistance, and endothelial function, may be at least partially causal.[25–27,43] Additionally, several studies in animal models have demonstrated that overfeeding in the first few days of life led to long-term obesity, perhaps by programming of the developing brain or the endocrine system.[28,29,44,45] These results should be contrasted with other studies showing an increased risk for coronary heart disease with low weight at birth and during infancy.[20,23,24] Most of these studies, however, did not specifically test the association of coronary heart disease with patterns of weight gains but rather with body weight at one point in infancy, which depends both on previous weight and weight gain. In interpreting the results of the present study, it should be emphasized that in humans, the weight change from birth to age 8 days cannot be considered as a true "growth parameter." Weight changes during this period mainly reflect the amount of formula ingested, which in turn could be influenced by a number of factors, including minor illnesses, perinatal depression, or slow meconium passage. Also, weight changes during this period are likely influenced by the degree of reduction in total body water, which is affected by mild overhydration or underhydration at the time of delivery. If confirmed by others and if in part causal, the present findings may lead to short interventions in infants to prevent long-term development of obesity. Because the prevalence of obesity continues to increase worldwide and its prevention and treatment are frequently unsuccessful,[1–5] new strategies based on a life-course approach may be useful to prevent obesity and related cardiovascular risk factors.

The present study confirms the previously reported associations of adult overweight status with weight gain in the first few months of life.[17,18] The life-course plot (Figure 2), however, suggests that the first week of life may be particularly sensitive. The present study also confirms the association of adulthood overweight with birth weight,[21,22] maternal overweight,[46] and increasing age of the subject.[1] Unlike what has been described in a nationally representative European American sample of the same age group, in the present sample, women were less likely to be overweight than men, and overweight was not associated with income.[47] Some of the adjusted analyses, but not the unadjusted analysis, revealed an increased risk for overweight in individuals assigned to the soy-based compared with the cow milk–based formula (Tables 2 and 3). This incidental finding should be taken with caution because of the inconsistency in results between analytical models and the borderline level of statistical significance, but it suggests that soy-based formula should be further investigated as a possible risk factor for overweight.

The present study had some limitations. Early cardiovascular disease could not be assessed by telephone interview in this sample of relatively young adults. Therefore, the present data do not provide information on the cardiovascular consequences of the association between early infancy weight

gain and adulthood obesity. Another limitation of the present study was the low prevalence of obesity and overweight. The prevalence of overweight was lower in this sample (32%) than in the general population of European Americans in this age range (55%) based on measured rather than self-reported weight and height,[5] which suggests underreporting of overweight in the present sample. Because it is unlikely that the presence or magnitude of underreporting was associated with absolute weight gain during the first week of life, this limitation likely resulted in a nondifferential misclassification, thus resulting in a bias toward the null hypothesis and an underestimation of the true effect size. Alternatively, the low prevalence of overweight and obesity in this sample reflects the relatively high socioeconomic status of the study subjects,[37] because the source population included many infants born to students and young faculty at the University of Iowa. The relatively small number of subjects classified as obese (BMI $\geq$30 kg/m^2) was insufficient to perform meaningful analyses, and the analyses are reported with overweight status (BMI $\geq$25 kg/m^2) as the outcome. Although not statistically significant, the direction of the associations was similar with the small number of obese subjects (data not shown). Birth weight was reported by the mother, but a significant reporting error is unlikely because it was assessed only 8 days after delivery. Should such reporting error have occurred, it would be unlikely to be associated with the outcome, which took place several decades later. Therefore, such bias would also have led to an underestimation of the effect size. Introduction of complementary foods after 28 days of life may have confounded the association of adult overweight with weight gain during the first 112 days of life but not with weight gain in the first week of life. The use of z scores obtained from smoothed cross-sectional reference data to model longitudinal data are controversial and has its limitations. These limitations, in the models that used z scores, may explain in part the large differences in ORs between the unadjusted and adjusted analyses and why, in the unadjusted analysis, the association of change in z score with adult overweight was not significant; however, after adjustment for important confounding factors, the results with absolute value of weight change or z scores were similar. Because of the characteristics of the sample, the present findings cannot be generalized to non-European American individuals or to breastfed infants, and our conclusions only apply to formula-fed infants. The relatively low rate of complete data (72%) was also of concern but is not unusual for a birth cohort with follow-up over 3 decades.

The study also had unique strengths. We used a life-course plot to identify potentially sensitive or critical periods of weight gain for the development of obesity[40] rather than arbitrarily chosen periods. By plotting the standardized β-coefficients of a multiple logistic regression that included several WAZ values measured during infancy, adjusted for each other and for important confounding variables, this method is the first, to the best of our knowledge, to allow identification, based on data, of potentially critical periods of weight gain for adult outcomes. One of the limitations of this method is the possibility that the addition of an observation between 2 observations may modify the observed slope and therefore the interpretation of the plot. Consequently, to provide useful information, this method assumes that measurements are close to one another, as described in detail by Cole.[40] In the present study, this assumption was met, and therefore this limitation is unlikely to have played an important role. Compared with breastfeeding, formula feeding has been associated with more rapid absolute weight gain in early infancy[30,31] and with obesity in adolescence,[32,33] but because the present study was limited to exclusively formula-fed subjects, our finding cannot be explained by infant feeding mode. Additionally, all infant measurements other than birth weight were performed prospectively as part of a rigorous research protocol.

In conclusion, the present study demonstrates a significant increase in the risk of overweight status in adulthood associated with increasing weight gain during the first week of life. This finding may have important research and public health implications at a time when obesity prevention is becoming a global public health priority to reduce cardiovascular and other obesity-related diseases.

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Disclosure

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References

1. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA*. 2002;288:1723–1727.
2. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999–2000. *JAMA*. 2002;288:1728–1732.
3. WHO Consultation on Obesity (1999: Geneva, Switzerland). Obesity: preventing and managing the global epidemic: report of a WHO consultation. Geneva, Switzerland: World Health Organization; 2000.
4. Lobstein T, Baur L, Uauy R. Obesity in children and young people: a crisis in public health. *Obes Rev*. 2004;5(suppl 1):4–85.
5. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA*. 2004;291:2847–2850.
6. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol*. 2002;31:285–293.
7. Oken E, Gillman MW. Fetal origins of obesity. *Obes Res*. 2003;11:496–506.
8. Dietz WH. Critical periods in childhood for the development of obesity. *Am J Clin Nutr*. 1994;59:955–959.
9. Stettler N, Bovet P, Shamlaye H, Zemel BS, Stallings VA, Paccaud F. Prevalence and risk factors for overweight and obesity in children from Seychelles, a country in rapid transition: the importance of early growth. *Int J Obes Relat Metab Disord*. 2002;26:214–219.

10. Stettler N, Zemel BS, Kumanyika S, Stallings VA. Infant weight gain and childhood overweight status in a multicenter, cohort study. *Pediatrics*. 2002;109:194–199.
11. Toschke AM, Grote V, Koletzko B, von Kries R. Identifying children at high risk for overweight at school entry by weight gain during the first 2 years. *Arch Pediatr Adolesc Med*. 2004;158:449–452.
12. Gunnarsdottir I, Thorsdottir I. Relationship between growth and feeding in infancy and body mass index at the age of 6 years. *Int J Obes Relat Metab Disord*. 2003;27:1523–1527.
13. Monteiro PO, Victora CG, Barros FC, Monteiro LM. Birth size, early childhood growth, and adolescent obesity in a Brazilian birth cohort. *Int J Obes Relat Metab Disord*. 2003;27:1274–1282.
14. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study [published erratum appears in *BMJ*. 2000;320:1244]. *BMJ*. 2000;320:967–971.
15. Eid EE. Follow-up study of physical growth of children who had excessive weight gain in first six months of life. *BMJ*. 1970;2:74–76.
16. Tanaka T, Matsuzaki A, Kuromaru R, Kinukawa N, Nose Y, Matsumoto T, Hara T. Association between birthweight and body mass index at 3 years of age. *Pediatr Int*. 2001;43:641–646.
17. Stettler N, Kumanyika SK, Katz SH, Zemel BS, Stallings VA. Rapid weight gain during infancy and obesity in young adulthood in a cohort of African Americans. *Am J Clin Nutr*. 2003;77:1374–1378.
18. Gasser T, Ziegler P, Seifert B, Molinari L, Largo RH, Prader A. Prediction of adult skinfolds and body mass from infancy through adolescence. *Ann Hum Biol*. 1995;22:217–233.
19. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth M. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *Br Med J*. 1989;298:564–567.
20. Osmond C, Barker DJ, Winter PD, Fall CH, Simmonds SJ. Early growth and death from cardiovascular disease in women. *BMJ*. 1993;307:1519–1524.
21. Curhan GC, Chertow GM, Willett WC, Spiegelman D, Colditz GA, Manson JE, Speizer FE, Stampfer MJ. Birth weight and adult hypertension and obesity in women. *Circulation*. 1996;94:1310–1315.
22. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Ascherio AL, Stampfer MJ. Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation*. 1996;94:3246–3250.
23. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early growth and coronary heart disease in later life: longitudinal study. *BMJ*. 2001;322:949–953.
24. Forsen TJ, Eriksson JG, Osmond C, Barker DJ. The infant growth of boys who later develop coronary heart disease. *Ann Med*. 2004;36:389–392.
25. Singhal A, Cole TJ, Fewtrell M, Deanfield J, Lucas A. Is slower early growth beneficial for long-term cardiovascular health? *Circulation*. 2004;109:1108–1113.
26. Singhal A, Cole TJ, Lucas A. Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials. *Lancet*. 2001;357:413–419.
27. Singhal A, Fewtrell M, Cole TJ, Lucas A. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. *Lancet*. 2003;361:1089–1097.
28. Plagemann A, Harder T, Rake A, Voits M, Fink H, Rohde W, Dorner G. Perinatal elevation of hypothalamic insulin, acquired malformation of hypothalamic galaninergic neurons, and syndrome X–like alterations in adulthood of neonatally overfed rats. *Brain Research*. 1999;836:146–155.
29. Waterland RA, Garza C. Early postnatal nutrition determines adult pancreatic glucose- responsive insulin secretion and islet gene expression in rats. *J Nutr*. 2002;132:357–364.
30. Dewey KG. Nutrition, growth, and complementary feeding of the breastfed infant. *Pediatr Clin North Am*. 2001;48:87–104.
31. Baker JL, Michaelsen KF, Rasmussen KM, Sorensen TI. Maternal prepregnant body mass index, duration of breastfeeding, and timing of complementary food introduction are associated with infant weight gain. *Am J Clin Nutr*. 2004;80:1579–1588.
32. von Kries R, Koletzko B, Sauerwald T, von Mutius E, Barnert D, Grunert V, von Voss H. Breast feeding and obesity: cross sectional study. *BMJ*. 1999;319:147–150.
33. Gillman MW, Rifas-Shiman SL, Camargo CA Jr, Berkey CS, Frazier AL, Rockett HR, Field AE, Colditz GA. Risk of overweight among adolescents who were breastfed as infants. *JAMA*. 2001;285:2461–2467.
34. Fomon SJ, Thomas LN, Filer LJ Jr, Ziegler EE, Leonard MT. Food consumption and growth of normal infants fed milk-based formulas. *Acta Paediatr Scand Suppl*. 1971;223:1–36.
35. Fomon SJ, Ziegler EE, Nelson SE, Edwards BB. Requirement for sulfur-containing amino acids in infancy. *J Nutr*. 1986;116:1405–1422.
36. Strom BL, Schinnar R, Ziegler EE, Barnhart KT, Sammel MD, Macones GA, Stallings VA, Drulis JM, Nelson SE, Hanson SA. Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. *JAMA*. 2001;286:807–814.
37. Fomon SJ, Nelson SE. Size and growth. In: Fomon SJ, ed. *Nutrition of Normal Infants.* St. Louis, Mo: Mosby; 1993:36–84.
38. Cole TJ. The LMS method for constructing normalized growth standards. *Eur J Clin Nutr*. 1990;44:45–60.
39. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL. CDC growth charts: United States. *Adv Data*. 2000;No. 314:1–27.
40. Cole TJ. Modeling postnatal exposures and their interactions with birth size. *J Nutr*. 2004;134:201–204.
41. Stata Corporation. *Stata 7 Reference Manual Extract : Release 7*. College Station, Tex: Stata Press; 2001.
42. Deleted in proof.
43. Singhal A, Farooqi IS, O'Rahilly S, Cole TJ, Fewtrell M, Lucas A. Early nutrition and leptin concentrations in later life. *Am J Clin Nutr*. 2002;75:993–999.
44. Plagemann A, Harder T, Rake A, Waas T, Melchior K, Ziska T, Rohde W, Dorner G. Observations on the orexigenic hypothalamic neuropeptide Y–system in neonatally overfed weanling rats. *J Neuroendocrinol*. 1999;11:541–546.
45. Plagemann A, Rake A, Harder T, Melchior K, Rohde W, Dorner G. Reduction of cholecystokinin-8S-neurons in the paraventricular hypothalamic nucleus of neonatally overfed weanling rats. *Neurosci Lett*. 1998;258:13–16.
46. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. *N Engl J Med*. 1997;337:869–873.
47. Zhang Q, Wang Y. Socioeconomic inequality of obesity in the United States: do gender, age, and ethnicity matter? *Soc Sci Med*. 2004;58:1171–1180.