

Can infant feeding choices modulate later obesity risk?^{1–5}

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ABSTRACT

Since the concept of lasting programming effects on disease risk in human adults by the action of hormones, metabolites, and neurotransmitters during sensitive periods of early development was proposed >3 decades ago, ample supporting evidence has evolved from epidemiologic and experimental studies and clinical trials. For example, numerous studies have reported programming effects of infant feeding choices on later obesity. Three meta-analyses of observational studies found that obesity risk at school age was reduced by 15–25% with early breastfeeding compared with formula feeding. We proposed that breastfeeding protects against later obesity by reducing the occurrence of high weight gain in infancy and that one causative factor is the lower protein content of human milk compared with most infant formula (the early protein hypothesis). We are testing this hypothesis in the European Childhood Obesity Project, a double-blind, randomized clinical trial that includes >1000 infants in 5 countries (Belgium, Germany, Italy, Poland, and Spain). We randomly assigned healthy infants who were born at term to receive for the first year infant formula and follow-on formula with higher or lower protein contents, respectively. The follow-up data obtained at age 2 y indicate that feeding formula with reduced protein content normalizes early growth relative to a breastfed reference group and the new World Health Organization growth standard, which may furnish a significant long-term protection against later obesity. We conclude that infant feeding practice has a high potential for long-term health effects, and the results obtained should stimulate the review of recommendations and policies for infant formula composition. *Am J Clin Nutr* 2009;89(suppl):1S–7S.

INTRODUCTION

Metabolic factors acting during limited and sensitive time periods of pre- and postnatal development can induce lasting effects on health and disease risk in later life up to old age, a phenomenon named *programming* or *metabolic programming* (1). The term programming was first introduced into the scientific literature by Günter Dörner, Professor and Chairman of the Institute of Experimental Endocrinology at Humboldt University, Berlin, Germany, >30 y ago (2). In his article, he proposed that concentrations of hormones, metabolites, and neurotransmitters during early development can preprogram brain development and functional disorders in human adults, reproduction,

and metabolism (3). Dörner also suggested that genetics and environment interact during early development to determine health outcomes in adulthood, an hypothesis that was confirmed by experimental data (1, 4–6). The early programming or early developmental plasticity hypothesis became more widely known after the publication of many epidemiologic studies showing an association between early markers of growth and the risks of hypertension, diabetes, and coronary heart disease in adult life (7–10).

There is an increasing interest in the kinetics of early growth and its possible consequences because high early weight gain in the first 1–2 y of life is associated with later adverse health outcomes (1, 11), such as increased blood pressure (12), increased overweight and body fat deposition (13–16), and increased risk of diabetes (17). Observational data cannot firmly

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³ This article does not necessarily reflect the views of the Commission of the European Communities and in no way anticipates the future policy in this area.

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establish causality because it is difficult to exclude residual confounding, but infant growth patterns are potentially modifiable by infant feeding practices. Therefore, opportunities exist for randomized clinical trials that evaluate the long-term programming effects of infant feeding and the potential preventive application for enhancing long-term health, well-being, and performance. Here we review some aspects of an ongoing randomized controlled trial that were recently reported (18). This trial is part of the European Early Nutrition Programming Project (<http://www.metabolic-programming.org>), the world's largest research collaboration on metabolic programming that brings together ≈ 40 research groups from across Europe to combine epidemiologic, experimental, and clinical trial methodology to study programming effects.

FEEDING IN INFANCY AND THE LATER RISK OF OBESITY

Obesity in children shows an alarming increase of both prevalence and severity in affluent as well as in less-privileged populations worldwide and is thus considered a global epidemic (19–21). Obesity in children is associated with serious short- and long-term adverse effects on the quality of life, performance, long-term health, and life expectancy, as well as with high financial burdens due to loss of productivity and the ensuing costs for health care and social support systems. It is therefore of great importance to develop and implement an effective therapeutic intervention for obese children, but the efficacy of currently available treatment strategies is less than satisfactory, and costs tend to be high (22). A Cochrane review of therapeutic interventions in childhood obesity found that there is no conclusive evidence on the effects of treatment strategies and their components (23). If options for effective treatment at reasonable costs are limited, primary prevention of obesity becomes even more important. Improvement of infant feeding might be one strategy that could contribute to reducing obesity risk in later life (1, 18).

EARLY GROWTH AND LATER RISK OF OBESITY

In animals, restriction of food intake for 3 wk was shown by McCance and Widdowson to permanently reduce body size up to adulthood if the food restriction was applied during early development, whereas no permanent effects were indicated if animals were exposed to food restriction at a later age. This represents an example of metabolic programming acting only during a sensitive period of early development (24). High birth weight of human infants is associated with an increased risk of later obesity (25, 26), which may be due to both genetic factors and early programming by the intrauterine environment. A number of studies also show that high postnatal weight gain increases the risk of later obesity (27–31). We evaluated growth measures of a group of 4235 German children aged 5–6 y who participated in the obligatory school entry health examination in the state of Bavaria, Germany, and for whom data on early weight, length, body mass index (BMI; in kg/m^2), and Ponderal index evaluation were available from the measurements taken during the preventive health care checks offered to all children and obtained at birth and at 6, 12, and 24 mo (13). Overweight at school entry was assessed according to sex- and age-specific

BMI cutoffs. Growth measures in early life were analyzed as possible predictors of later overweight by using receiver operating curves (ROCs) and predictive values. Higher weight gain from birth to age 2 y was associated with a higher prevalence of overweight at school entry (**Figure 1**). For all variables tested, the highest areas under the ROC (AUC) were observed for the gain from birth to age 24 mo. The AUC decreased in order from weight gain (0.76) to BMI gain (0.70) to length gain (0.58) ($P < 0.001$) (**Table 1**). The highest Youden index (sensitivity + specificity – 1) for weight gain from birth to 24 mo (41%) was attained for a cutoff of 9764 g, with a corresponding likelihood ratio of 2.39 and a positive predictive value of 19% despite an odds ratio of 5.7 (95% CI: 4.5, 7.1). We conclude that high weight gain during the first 24 mo is the best overall predictor of overweight at school entry, as compared with other anthropometric markers and time intervals.

In accordance with these results, many studies of other populations, summarized in 3 systematic reviews, concluded that rapid weight gain in infancy and in the first 2 y of life is a significant risk indicator for later adiposity (33–35). Thus, if infant feeding can be modified such that very high weight gain is prevented, a benefit with regard to reducing later obesity risk appears possible.

BREASTFEEDING AND OBESITY IN LATER LIFE

Many studies have shown that populations of breastfed infants grow slightly differently than do those of formula-fed infants, with formula-fed infants reaching a higher body weight and weight for length at 1 y of age (**Figure 2**) (37). A systematic review of 19 studies in affluent populations concluded that the cumulative difference in body weight amounts to ≈ 400 g less weight by the age of 12 mo in infants breastfed for 9 mo, and

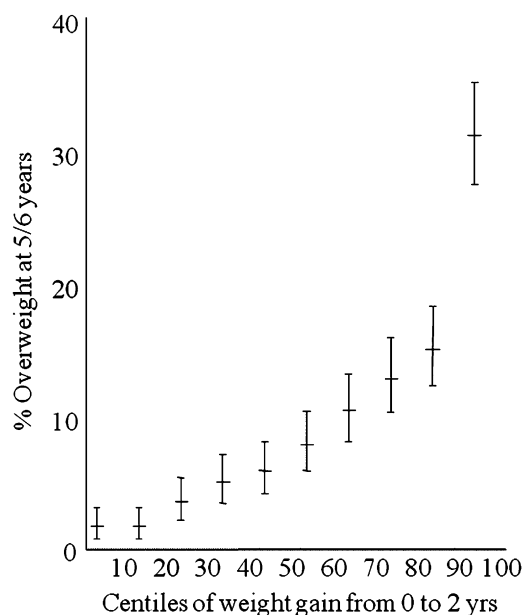


FIGURE 1. Higher weight gain from birth to age 2 y (centiles) is associated with a higher prevalence of overweight at school entry in 4235 children in Bavaria, Germany. Data from Toschke AM, Grote V, Koletzko B, von Kries R. Is weight gain during the first two years suitable to identify children at high risk for overweight at school entry? *Arch Pediatr Adolesc Med* 2004;158:449–52.

TABLE 1

Area under the receiver operating characteristic (ROC) curves, cutoffs, and sensitivity and specificity at the highest Youden index for early anthropometric measurement prediction of overweight at school age in 4235 children in Bavaria, Germany¹

Measure	Area under the ROC curve	Cutoff at highest Youden index ²	Sensitivity at highest Youden index	Specificity at highest Youden index
Age 0–6 mo				
Weight	0.63 (0.60, 0.66)	5100 g (19)	45 (40, 50)	74 (73, 76)
Length	0.51 (0.48, 0.55)	20 cm (4)	21 (17, 25)	83 (81, 84)
BMI ³	0.60 (0.57, 0.63)	5 (15)	43 (38, 48)	72 (70, 73)
Ponderal index ⁴	0.59 (0.53, 0.60)	0.2 (11)	32 (27, 37)	78 (76, 79)
Age 0–12 mo				
Weight	0.68 (0.65, 0.70)	6933 g (27)	68 (63, 72)	59 (58, 61)
Length	0.55 (0.52, 0.58)	26 cm (9)	66 (61, 71)	43 (42, 45)
BMI	0.63 (0.60, 0.66)	4 (20)	66 (62, 71)	53 (51, 55)
Ponderal index	0.57 (0.54, 0.60)	−0.3 (11)	64 (59, 69)	47 (45, 48)
Age 0–24 mo				
Weight	0.76 (0.74, 0.79)	9764 g (41)	70 (65, 75)	71 (69, 72)
Length	0.58 (0.55, 0.61)	39 cm (13)	45 (40, 50)	68 (66, 69)
BMI	0.70 (0.67, 0.72)	4 (31)	57 (52, 62)	74 (73, 75)
Ponderal index	0.61 (0.58, 0.64)	−0.5 (17)	44 (39, 49)	72 (71, 74)

¹ Weight gain from birth to age 2 y is the best predictor of overweight at school age (32). Data are given as values (95% CIs) unless otherwise indicated.

² (Sensitivity + specificity) − 1.

³ Calculated as weight in kilograms divided by the square of height in meters.

⁴ Calculated as weight in kilograms divided by the length in meters cubed.

as much as 600–650 g less weight at 1 y in infants that are breastfed for 12 mo (38). Given this rather large effect of infant feeding choices on infant weight gain, we aimed to study whether breastfeeding might also confer protection against later obesity risk.

We evaluated the effect of breastfeeding on the risk of obesity and overweight at school entry in a cross-sectional survey conducted in Bavaria, Germany (39). Data were collected on height and weight in 134,577 children who participated in the obligatory health examination at school entry, and BMI values were calculated. We determined the 90th- and the 97th centile values of German children aged 5 and 6 y, which we used as cutoffs to define overweight and obesity, respectively. In a subgroup of 13,345 children in 2 regions, early feeding, diet, and lifestyle factors were assessed by using responses to a questionnaire completed by parents. We included the data of 9357 children aged 5 and 6 y with German nationality in the final analysis. Children who were never breastfed had a higher prevalence than children who had been breastfed of both overweight (12.6% compared with 9.2%) and obesity (4.5% compared with 2.8%). A longer duration of breastfeeding after birth

was associated with a lower prevalence of later obesity: obesity prevalence was 3.8% for 2 mo of breastfeeding, 2.3% for 3–5 mo, 1.7% for 6–12 mo, and 0.8% for >12 mo (**Figure 3**). Similar relations were found with the prevalence of overweight (Figure 3). The protective effect of breastfeeding was not attributable to differences in social class or lifestyle, but remained significant after adjusting for confounding factors. Children who had been breastfed showed a significantly reduced adjusted odds ratio, as compared with those who were never breastfed, for both overweight (0.79, 95% CI: 0.68, 0.93) and obesity (0.75, 95% CI: 0.57, 0.98). Again, the adjusted odds ratios showed a significant inverse dose-response relation between duration of breastfeeding and overweight and obesity, which is compatible with a causal effect of breastfeeding or breast milk components on obesity reduction.

After publication of our research (39), a number of other investigators all over the world have also tested the relation

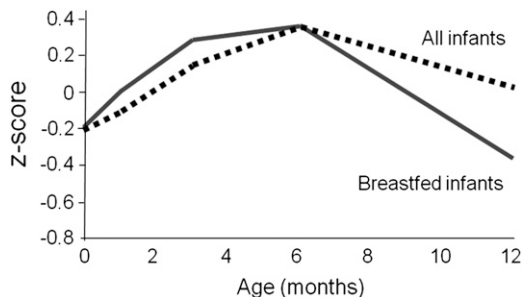


FIGURE 2. Weight for age (mean z scores plotted against the US National Center for Health Statistics reference) of infant boys in the breastfed subset and of all infants in ≈2500 boys from the 1993 birth cohort study in Pelotas, Brazil. Breastfed infants showed faster weight gain in the first 3 mo, but a relative decline thereafter, and were leaner at 1 y (36).

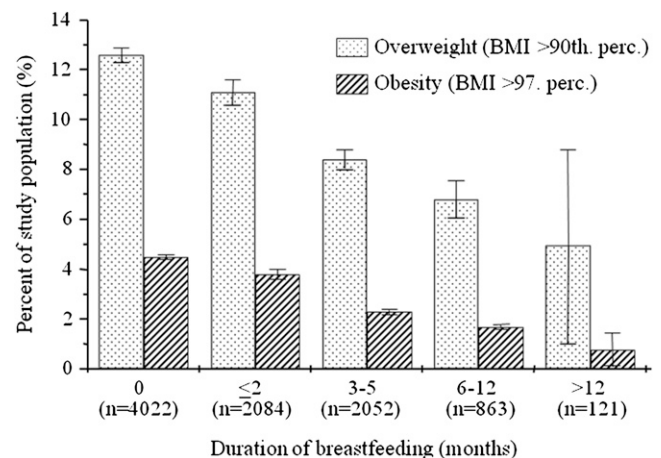


FIGURE 3. Longer duration of breastfeeding in infancy is associated with a lower prevalence of both overweight and obesity at school entry in 9357 children in Bavaria, Germany (39). perc., percentile.

between breastfeeding and later obesity in different cohort studies. We evaluated published epidemiologic studies (cohort, case-control, and cross-sectional studies) on the effects of early feeding mode on later overweight and obesity in a systematic review and meta-analysis (40). In our evaluation, we included only studies that adjusted for at least 3 of the relevant confounding or interacting factors: birth weight, parental overweight, parental smoking, dietary factors, physical activity, and socioeconomic status. Parental education was accepted as an appropriate indicator of socioeconomic status. Other inclusion criteria were as follows: comparable risk estimates as odds ratios or relative risks had to be reported; age at the last follow-up had to be between 5 and 18 y; feeding mode had to be assessed and reported; and obesity as an outcome had to be defined by the 90th, 95th, or 97th BMI percentiles to allow for comparison of the studies. If risk estimates were calculated for different percentile values in a particular study, the estimate for the highest percentile value was included in the meta-analysis. Electronic databases were searched and reference lists of relevant articles were checked. Calculations of pooled estimates were conducted in fixed-effects and random-effects models, and heterogeneity was tested by Q-test. Funnel plots and a linear regression method were used to test for publication bias. Included were 9 studies with >69,000 children. The result of the meta-analysis showed that breastfeeding was associated with a significant reduction of the risk of obesity in childhood and with an adjusted odds ratio of 0.78 (95% CI: 0.71, 0.85) in the fixed model. A dose-dependent effect of breastfeeding duration on the prevalence of obesity was reported in 4 studies. Funnel plot regression gave no indication of publication bias.

One year later, Harder et al (41) obtained very similar results in a meta-analysis with different inclusion criteria and a much larger number of studies that were evaluated. These authors found that breastfeeding was associated with a significantly reduced pooled adjusted odds ratio for later obesity of 0.75 (95% CI: 0.68, 0.82). Harder et al (41) also reported a significant relation between duration of breastfeeding and later obesity, in which each additional month of breastfeeding resulted in a 4% lower obesity prevalence at later ages. Owen et al (42) published a meta-analysis that confirmed a protective effect of breastfeeding in an even larger number of studies that met their inclusion criteria, but these authors reported a smaller effect size with an odds ratios of 0.87 (95% CI: 0.85, 0.89). Seventy-five percent of the result obtained in their evaluation could be attributed to a single large study in the United States of the Women, Infants, and Children Program, which supports low-income women and children. It has been proposed that specific aspects in this cohort study, such as a high degree of mixed feeding, might have led to results that differ from other cohort studies, and hence these results might not be representative of other breastfed populations. Whereas all these studies are observational in nature and hence cannot exclude residual confounding, the Probit study in Belarus has cluster randomized hospitals to a program of breastfeeding promotion or no active intervention, and this study showed a significantly longer duration of breastfeeding with the intervention (43). When the children were revisited at the age of 6.5 y, measures of obesity in the intervention and control groups were not different. However, this study did not compare breastfeeding and formula feeding because almost all children had been breastfed. Moreover, the

breast-milk substitutes used in Belarus differ from those in other parts of the world, the prevalence of obesity was rather low in this population, and the study was underpowered to detect effects of breastfeeding on obesity. Thus, the Probit study does not allow final conclusions on the effects of infant feeding on later obesity.

We conclude that breastfeeding is associated with a modest but consistent protective effect against later obesity in numerous observational studies and in 3 meta-analyses. These data should encourage the promotion, protection, and support of breastfeeding. The underlying mechanisms for possible protection by breastfeeding are not known and should be explored. Understanding of these mechanisms may strengthen the conclusions on the protective effects of breastfeeding, and, moreover, this knowledge might help to extend the protective effects to infants who are not breastfed for long periods by improving the practice of feeding formula and complementary foods.

WHY IS BREASTFEEDING ASSOCIATED WITH A LOWER RISK OF OBESITY IN LATER LIFE?

Breastfeeding and bottle feeding of infants differ in numerous aspects, for example, in the content of nutrients and of non-nutrient substances such as bioactive factors, the mode of feeding and infant suckling behavior, and in the mother-infant interaction. Thus, a large number of hypotheses can be raised to potentially explain the observed protective effect of breastfeeding against later obesity. Whereas protection by any breastfeeding and by a longer duration of breastfeeding persists in many studies after adjustment for relevant confounders, one cannot fully exclude potential residual confounding in observational studies. It is not feasible to randomly assign healthy babies to breastfeeding or formula feeding for ethical and practical reasons, and hence indisputable proof for a causal protective effect of breastfeeding from a randomized clinical trial cannot be obtained. However, given the modest but consistent protective effects in many studies, as well as the observed dose-response relation between longer duration of breastfeeding and greater reduction of later obesity, potential underlying mechanisms of breastfeeding should be evaluated.

It appears possible that the marked differences in feeding behavior and mother-child interaction between populations of breastfed and formula-fed infants are of importance. Formula-fed babies show a different suckling pattern, a lower frequency of meals, and longer time intervals between meals than typically found in breastfed infants (44, 45). In a prospective study of healthy infants, formula-fed babies aged 6 wk achieved a 20–30% higher feeding volume than breastfed infants, and they had fewer meals and fewer nightly feedings at 4 mo of age (46). In another study, early feeding patterns were predictive of BMI at 3 y of age: infants who showed high-pressure sucking measured at 2 and 4 wk of age, which indicates a more vigorous feeding style, showed a higher degree of adiposity at toddler age (47). Thus, the early feeding pattern may be relevant to later obesity risk.

Although infant formula shows a stable composition and organoleptic properties, human milk is remarkably variable in nutrient content as well as in taste and smell from day to day, and even from meal to meal, depending on the stage (duration) of lactation, maternal diet, metabolic state of the lactating woman, the volume of milk consumed by the baby, and the extent of breast

expression (48). It has been proposed that early exposure to taste and smell may enhance the later acceptance and consumption of foods with similar properties (49), and hence breastfeeding, by way of exposing babies to a variety of flavors, might program infants to somewhat different food selection and dietary habits in later life compared with formula-fed infants. This possibility deserves to be explored further.

It has often been suggested that breastfeeding enhances the emotional bonding of mother and child, perhaps mediated by a more intensive skin contact and by the stimulation of maternal oxytocin release with infant suckling (50, 51). Women who breastfeed were reported to show a lesser neuroendocrine response to stressors, increased parasympathetic nervous system modulation, lower perceived stress levels, and fewer depressive symptoms than women who formula-feed, but a possible influence of confounding factors related to both of these outcomes as well as to the initial decision to breastfeed must be taken into account (50, 51). Nonetheless, such neuroendocrine and psychological factors associated with breastfeeding might well have implications for the later interaction between mother and child and for associated health-related behavior. Testing long-term behavioral effects of breastfeeding in humans may pose considerable methodologic challenges, but to some extent animal models might help to gain insights into these interesting questions.

THE EARLY PROTEIN HYPOTHESIS

Whereas feeding infant formula cannot mimic feeding at the breast, the composition of infant formula can potentially be made more similar to the composition of human milk. Differences in substrate supply between human milk or infant formula might indeed play a role in programming obesity risk, and we proposed previously that the greater weight gain in formula-fed infants, relative to breastfed infants, is caused at least in part by the different intakes of metabolizable protein (52).

Most infant formulas have a slightly higher energy density (kcal/100 ml) than typical human milk, and energy intakes per kilogram of body weight in formula-fed infants aged 3–12 mo were reported to be ≈ 10 –18% higher than those of breastfed babies (53). Even much larger is the difference in protein supply per kilogram of body weight, which is 55–80% higher in formula-fed babies than in breastfed infants (54). High-protein supplies during pregnancy were shown to decrease energy expenditure and to increase later adiposity in rodents (55). Other studies in rodents showed that a high protein and nutrient supply in the postnatal period induced increased body fat in adult animals (56) and led to a 10–40% higher body weight in adulthood (57). A high protein intake in excess of metabolic requirements may enhance the secretion of insulin and insulin-like growth factor I (IGF-I) (**Figure 4**). Infants fed cow-milk protein-based infant formula were shown to have far higher postprandial concentrations of insulin on day 6 of life than breastfed infants (58). High insulin and IGF-I values can enhance growth during the first 2 y of life (59, 60) and adipogenic activity and adipocyte differentiation (61) (**Figure 4**). Moreover, high protein intakes may also lead to decreased human growth hormone secretion and hence to reduced lipolysis. Epidemiologic studies found that high protein intakes in early childhood, but not high intakes of energy, fat, or carbohydrates, was predictive of an early occurrence of the adiposity rebound and a high BMI in childhood,

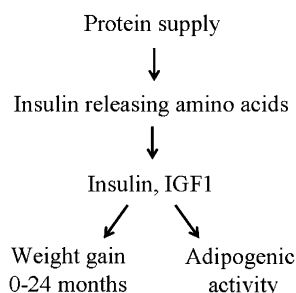


FIGURE 4. The early protein hypothesis: a high protein intake with infant formula feeding, in excess of metabolic requirements, might induce increased circulating concentrations of insulin-releasing amino acids, which in turn might stimulate the secretion of insulin and insulin-like growth factor I (IGF1), thereby inducing an increased weight gain during the first 2 y of life as well as increased adipogenic activity.

corrected for parental BMI (62–65). Thus, the markedly higher protein intake with infant formula feeding, as compared with the protein supply in breastfed babies, may play a role in predisposing infants to an increased obesity risk in later life (the early protein hypothesis) (1).

Although prospective epidemiologic and experimental studies can provide arguments to support the early protein hypothesis, the real effect can be tested only in a prospective human intervention trial. With financial support by the European Commission's 5th Framework Research Program and 6th Framework Research Program, the European Childhood Obesity Project (<http://www.metabolic-programming.org>) was set up to test, in a randomized double-blind intervention trial, whether higher or lower protein intakes during the first year of life influence growth until the age of 2 y as well as obesity risk at the later school age. This multicenter, randomized clinical trial is being conducted in 5 European countries (Belgium, Germany, Italy, Poland, and Spain) that differ substantially in the practice of infant and young child feeding and in their prevalence of adult obesity. This fact offers the opportunity to combine a multicenter intervention trial on infant formulas that differ in their balance of protein and fat (provided by Bledina, Steenvoorde, France) with an epidemiologic observation study that can assess overall dietary protein intakes and thus may allow for an additional external validation. We hope that this strategy will allow for assessment of the effects of variables that differ substantially within Europe, as well as for assessment of the effects of the randomized controlled intervention. A breastfed reference group is included at each center to allow for an epidemiologic comparison of the effects of breastfeeding and formula feeding.

We chose growth from birth to age 2 y as the primary outcome variable on the basis of our previous findings that this measure is a predictive early biomarker of later obesity risk (13). A number of further measures are also assessed, including detailed data on infant diet, infant and lifestyle and behavior, biochemical and endocrine markers, and markers of renal function. Randomization and data collection are performed by Internet-based electronic case report forms that use specially developed information technology architecture with a central database and 12 remote data-entry stations as well as dedicated software that allows for secure data protection. Effective mechanisms for quality assurance have been established. Data input and transfer to the central database are supervised by a contract research organization participating in the project.

Recruitment for the intervention and follow-up of all participating subjects until the age of 2 y has been successfully completed. The first evaluation of data obtained indicates that the group of infants randomly assigned to formula with a higher protein content showed a significantly higher body weight and BMI at the age of 2 y than the group of infants randomly assigned to a lower protein supply (66). Provision of the lower protein content with formula led to normalized growth measures at 2 y, relative to the breastfed reference group. Further data evaluation is ongoing, and the subjects in the trial are being monitored at higher ages to explore both the long-term safety and the potential benefits of the intervention at preschool and school age. However, even the early results obtained might lead to a review of recommendations for infant feeding and policy and regulatory guidance, as well as product design, because one aims for physiologic growth of formula-fed populations similar to that of healthy breastfed populations (67), and there is no known advantage of growth patterns of formula-fed babies that deviates from those of breastfed populations. Therefore, a protein content of standard infant formula near 1.8 g/100 kcal is desirable. (Other articles in this supplement to the Journal include references 68–75.)

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The authors' responsibilities were as follows—BK: conceived the concept of the European Childhood Obesity Trial, acts as the principal investigator and guarantor, acts as the coordinator of the Childhood Obesity Project (CHOP) and the Early Nutrition Programming Project (EARNEST, <http://www.metabolic-programming.org>), and was the principal writer of this manuscript; RvK and VG: performed the statistical evaluation of the CHOP trial; RCM, JES, SS, MG, JB, HD, DG, AD, AS, and JPL: contributed to the conduct of the study; and M-FRC: counseled on standardized anthropometric measures and training of study personnel. All other authors critically read the manuscript. The authors had no conflicts of interest and no disclosures to declare.

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