PROTEIN INTAKE IN THE FIRST YEAR OF LIFE: A RISK FACTOR FOR LATER OBESITY?

The EU Childhood Obesity Project

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Abstract: Effective strategies for primary prevention are urgently needed to combat the rapidly increasing prevalence of childhood obesity. Evidence accumulates that early nutrition programmes later obesity risk. Breast feeding reduces the odds ratio for obesity at school age, adjusted for biological and sociodemographic confounding variables, by some 20-25 %. We propose that the protective effect of breast feeding is related in part by the induction of a lower weight gain in infancy, which is related to differences in substrate intake. Protein intake per kg bodyweight is some 55-80 % higher in formula fed than in breast fed infants. We hypothesize that high early protein intakes in excess of metabolic requirements enhance weight gain in infancy and increase later obesity risk (the "early protein hypothesis"). The European Childhood Obesity Programme tests this hypothesis in a randomized double blind intervention trial in 1150 infants in five European centres. Infants that are not breast fed are randomized to formulae with higher or lower protein content and followed up to school age. If an effect of infant feeding habits on later obesity risk should be established, there is great potential for effective preventive intervention with a significant potential health benefit for the child and adult population.

Key words: Insulin; Insulin like growth factor I (IGF1); Metabolic Programming; Randomized clinical trial; European Commission Fifth Framework Programme;

1. THE NEED FOR OBESITY PREVENTION

Childhood obesity is now considered a global epidemic in view of the alarming increase of its prevalence and severity, not only in affluent but also in less privileged childhood populations worldwide (1,2). Serious short and long term consequences of childhood obesity arise in terms of damage to quality of life, performance, health and life expectancy. In addition, the size of the obesity epidemic is estimated to create huge costs for society due to loss of productivity and ensuing costs for health care and social security (1,2). Faced with the size of the problem, widely available and effective medical management of children that are already obese is needed, but at present the results of available treatments are far less than satisfactory, and costs are high (3). A recent Cochrane review on interventions for treating obesity in children found that no conclusions on the effects of treatment strategies and their components can be drawn with confidence (4).

Thus, in the present situation the emphasis must be put on development, evaluation and implementation of effective primary prevention of obesity. Some first evaluations are available on the efficacy of obesity prevention in children, even though the limited number of controlled trials available at this time allows only limited conclusions (5). Promising key strategies for prevention aim at modifying childhood behaviour to increase physical activity as a daily routine and to enhance health promoting dietary habits (1,2,5). In addition, new concepts evolve on prevention at a very early age. Already in the 1950s McCance and Widdowson observed that feeding conditions of animals during sensitive periods of early pre- and postnatal growth predetermined their weight in adulthood (6). This phenomenon, later called early nutritional or metabolic programming of adult health, has attracted renewed scientific attention. Today numerous experimental and epidemiological studies provide clear indications that metabolic events during critical time windows of pre- and postnatal development markedly modulate obesity risk in later life. Hence, modification of nutritional habits during early development may offer an opportunity for effective risk reduction of later obesity in populations. The potential practical relevance for obesity prevention is highlighted by a series of studies showing that breast fed individuals have a significantly lower obesity risk many years later than those who had been formula fed after

birth. Breast feeding reduced the odds ratio for obesity at school age, adjusted for a variety of biological and sociodemographic confounding variables, by some 20 to 25 % (8-11).

2. DOES BREAST FEEDING PROTECT AGAINST LATER OBESITY BY MODULATING CHILD BEHAVIOUR?

Elucidation of underlying mechanisms for the lesser obesity risk associated with breast feeding is important, because understanding of such mechanisms might offer opportunities for improvements of policy and practice of infant feeding regimens both for infants that are breast fed and for those that receive formula.

A number of hypotheses can be raised on potential causes. Even though the inverse relationship of both breast feeding and breast feeding duration with later obesity persists after adjustment for measurable confounding variables, residual confounding cannot be fully excluded. Since one cannot randomise healthy babies to feeding breast milk or formula for ethical and practical reasons, undisputable proof for a protective effect of breast feeding can hardly be obtained. However, the consistent results of many studies and the dose response effect between duration of breast feeding and later reduction of obesity risk observed in a number of studies make an effect of breast feeding highly likely (11).

Differences in feeding behaviour and mother-child-interaction between populations of breast and formula fed infants might have a role to play. Breast fed infants show a different suckling pattern and a higher suckling frequency (12,13). Breast fed infants seem to have greater degree of control on meal sizes and intervals than those fed formula. Sievers and co-workers monitored marked differences in feeding patterns, with a 20-30 % higher feeding volume of formula fed infants after 6 weeks of life as well as a smaller number of total meals and of nightly meals in bottle fed babies at 4 months of age (14). Such differences may modulate later body size. Agras and co-workers reported that early feeding patterns were predictive of body mass index at 3 years of age, with high-pressure sucking measured in the laboratory at 2 and 4 weeks of age (denoting a vigorous feeding style) associated with greater degree of adiposity in toddlers (15).

In contrast to infant formula, breast milk varies in taste and smell depending on maternal intake of diet and spices, and early taste experience in infancy has been shown to favour later consumption of foods with the same taste (16). Thereby, breast fed infants might be programmed to different food selection and dietary habits in alter life.

Moreover, breast feeding appears to enhance emotional bonding of the mother to her child, mediated in part by the stimulation of maternal oxytocin release by infant suckling, and breast feeding shown to lead to decreased neuroendocrine response to stressors and decreased negative mood in the mothers (17,18). These effects of breast feeding might well have repercussions on the interaction between mother and child and health related behaviours.

These and further behavioural hypotheses are plausible and attractive, but are difficult to test experimentally, thus for the time being they remain somewhat speculative.

3. ARE 'OBESITY PREVENTIVE' EFFECTS OF BREAST FEEDING RELATED TO EARLY GROWTH AND SUBSTRATE SUPPLY?

The mode of infant feeding at the breast cannot be copied with human milk substitutes, but if protective effects of breast feeding were related to compositional aspects of breast milk and to the nature of substrate supply, such benefits could potentially be extended also to formula fed populations by appropriate modifications of infant formula composition. Promising approaches can be deduced from studies evaluating physiological differences of breast and bottle fed infants.

Populations of formula fed infants show higher growth rates, with larger weight and length gains than infants fed formula (19). Based on a systematic review of 19 studies in affluent populations, Dewey concluded that by the age of 12 months, the cumulative difference in body weight amounts to approximately 400 g in infants breast-fed for 9 months and as much as 600-650 g in infants that are breast-fed for 12 months (20). This very large effect of the mode of feeding on weight gain must be expected to influence later obesity risk, based on our analysis of a large cohort study on 4235 children from Bavaria, southern Germany (21). We related overweight at school entry at school entry (age 5-7 years) to growth data obtained during the paediatric preventive

health checks at birth, 6 months, 12 months, and 24 months of age. High weight gain from birth to 24 months proved to be a strong predictor of later overweight. Children in the upper tertile of weight gain from birth to 2 years (weight gain over 24 months >9764 g) had an odds ratio of 5.7 (95% CI, 4.5-7.1) for overweight at school age relative to those with a

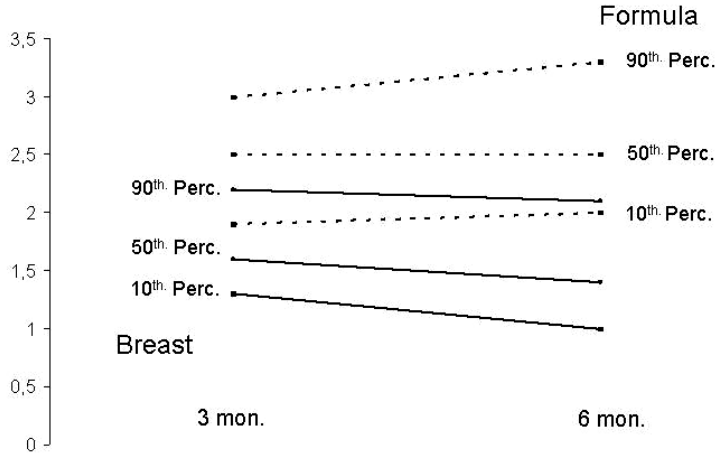

Fig. 1: Protein intake at ages 3 and 6 months (g/kg body weight, median and $90^{th}/10^{th}$ percentiles) in infants fed breast milk or infant formula (participants of the DONALD study [23])

lower early weight gain (21). Given this close relationship, we hypothesize that the protective effect of breast feeding against later obesity risk is based, at least in part, on its mediating effect on infant weight gain.

The degree of weight gain in infancy is influenced by genetic factors of the individual, birth weight, metabolic influences during pregnancy, health and disease (for example concurrent infections), and not the least dietary substrate supply. Infant formulae have a higher average caloric density (kcal/100 ml) than mean values for breast milk, and energy supplies per kg bodyweight to formula fed infants are 10-18 % higher than those to breast fed babies between 3 and 12 months of age (20). Even larger is the difference in protein intake per kg bodyweight, which is 55-80 % higher in formula than in breast fed infants (fig. 1) (22,23).

In animal studies, early nutrient supply was shown to programme later obesity risk. In rats, prenatal high protein exposure decreased

energy expenditure and increased later adiposity (24), and a high postnatal protein and nutrient supply led to higher adult body fat deposition (25) and increased adult weight by 10-40% (26).

A high protein intake in excess of metabolic requirements may enhance the secretion of insulin and insulin like growth factor 1 (IGF1). Indeed, infants fed formula had far greater postprandial levels of insulin on day six of life than infants fed cows' milk based formula (27). High insulin and IGF1 values can enhance both growth during the first 2 years of life (28) as well as adipogenic activity and adipocyte differentiation (29) (fig. 2). High protein intakes may also decrease human growth hormone (hGH) secretion and lipolysis.

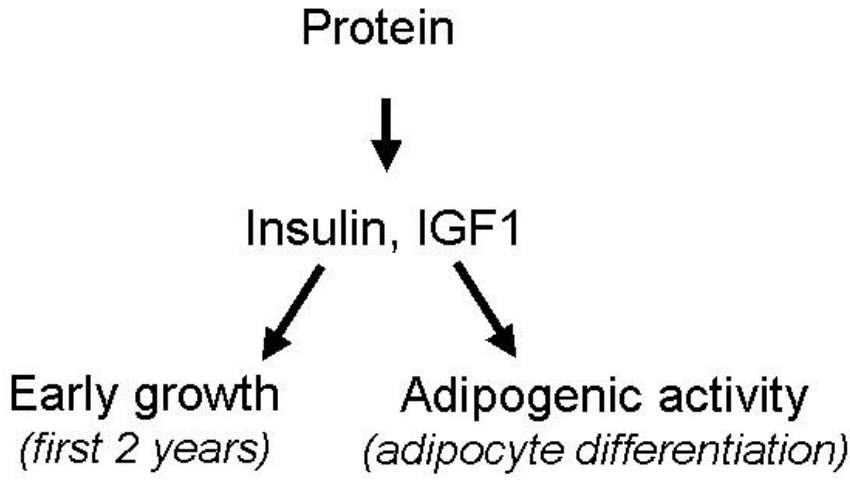

Fig. 2: High early protein intakes stimulate the secretion of insulin and insulin like growth factor 1 (IGF 1), which can enhance early growth and adipogenic activity.

Indeed, high protein intakes in early childhood, but not the intakes of energy, fat or carbohydrate, were significantly related to an early occurrence of adiposity rebound and to high childhood body mass index (BMI), corrected for parental BMI (30-32). Thus, we hypothesize that a high protein intake with infant formula, in excess of metabolic requirements, may predispose to an increased obesity risk in later life (early protein hypothesis) .

4. THE EUROPEAN CHILDHOOD OBESITY PROGRAMME

In addition to experimental approaches, human intervention studies are needed to test this "early protein hypothesis". The European Childhood Obesity Programme (www.childhood-obesity.org) funded by the European Commission's 5th Framework Research Programme has enrolled some 1150 infants after birth and aims at following them up through school age to test, in a randomized double blind intervention trial, whether variation in early protein intakes affects growth kinetics and later obesity risk. This trial is conducted in five European countries which differ substantially in their prevalence of adult obesity and also in the nutritional characteristics of the habitual diet of infants and children, in particular in protein supply with complementary feeding, i.e. Belgium (Co-ordinator Prof. Daniel Brasseur), Germany (Prof. Berthold Koletzko), Italy (Prof. Marcello Giovannini), Poland (Prof Jerzy Socha) and Spain (Dr. Ricardo Closa). Therefore the trial offers the opportunity to combine a multicentre intervention trial on infant formulae (kindly provided by Blédina SA, Steenvoorde, France) which differ in their balance of protein and fat, with an epidemiological observation study which can assess the balance of protein and fat in the overall early diet. This approach will enable us to assess the effect of variables which differ substantially within Europe, as well as allowing the intervention trial results to be analyzed within centres. The inclusion of a group of breast–fed infants in each centre will also allow an epidemiological comparison of the effects of breast feeding and formula feeding in the different countries. This approach will provide the opportunity for an external validation of the underlying hypothesis.

Growth from birth to age 2 years, a marker of later obesity risk, was chosen as the primary outcome variable. In addition, a variety of further variables are measured, including detailed data on diet, lifestyle and behaviour, biochemical and endocrine markers, markers of renal function, and others (Fig. 3). Randomisation and data collection are performed via the internet based on uniform electronic case report forms, using 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. Mechanisms for quality

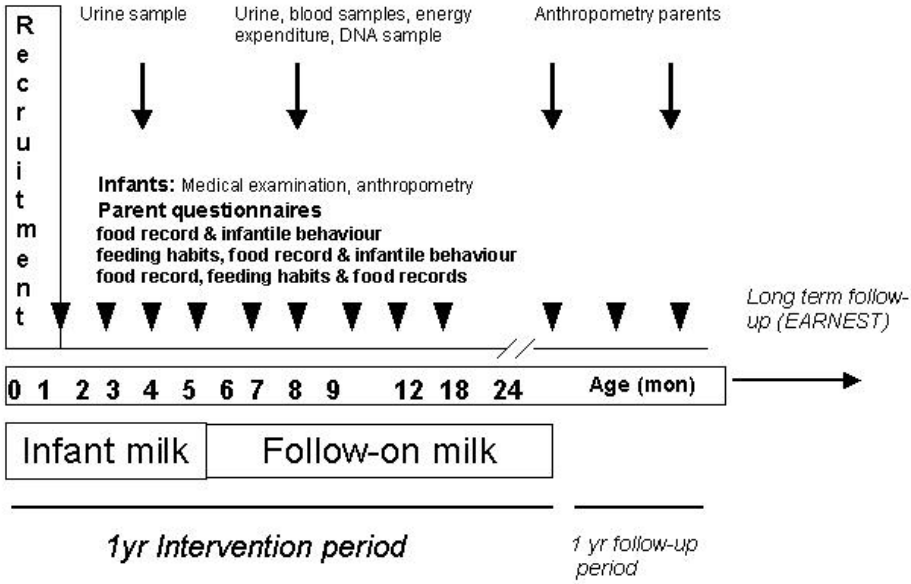

Fig. 3: Scheme of the study design of the European Childhood Obesity Programme. Infants are randomized to infant and follow-on formulae with higher or lower protein intakes from the neonatal period through the first year of life. Diet, behaviour, growth and a number of other variables are monitored during regular follow-up visits.

assurance have also been established. Data input and transfer to the central database are supervised by a contract research organization participating in the project.

The intervention trial started on 1st October 2002, and recruitment was completed on 30th June 2004. Following the study protocol and the requirements to report first results to the EU at the end of the first funding period, the study will be un-blinded in the second half of 2006 to allow for first data evaluations. However, participating children and their families will be invited for further follow-up in the project EARNEST (Early Nutrition programming of adult health, www.metabolic-programming.org) funded by the EU 6th Framework Programme.

In our view, the European Childhood Obesity Programme offers unique and exciting opportunities for evaluating the effects of early diet on long-term health in later life. If an effect of infant feeding habits on long-term growth, development of later body composition and obesity

risk is established, there is great potential for effective preventive intervention by modification of the composition and use of dietary products for infants. Thus, the expected results may have a very direct, simple application with a significant potential health benefit for the child and adult population.

5. ACKNOWLEDGMENTS

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REFERENCES

1. Koletzko B, Girardet J P, Klish W, Tabacco O. Obesity in children and adolescents worldwide: current views and future directions. J Ped Gastroenterol Nutr 2002; 35:S205-12.
2. Fisberg M, Baur L, Chen W, Nelson T, Koletzko B, Moreno L, Uauy R, Hoppin R, Lau D, Strauss R. Childhood Obesity - a global perspective. J Pediatr Gastro Nutr 2004;39:S678-87.
3. Koletzko B. Childhood obesity: time for treatment or prevention? Eur J Lipid Sci Technology 2004;106:287-288
4. Summerbell CD, Ashton V, Campbell KJ, Edmunds L, Kelly S, Waters E. Interventions for treating obesity in children (Cochrane review). The Cochrane library 2004; Issue 1
5. Campbell KJ, Waters E, O'Meara S, Kelly S, Summerbell C. Interventions for preventing obesity in children (Cochrane review). The Cochrane library 2004; Issue 1
6. Koletzko B, de la Guéronnière V, Toschke AM, von Kries R. Nutrition in children and adolescents in Europe: what is the scientific basis? Introduction. Brit J Nutr 2004;92,suppl 2:S67-73

7. Ashwell M (ed.). McCance & Widdowson. A scientific partnership for 60 years. London, The British Nutrition Foundation 1993.
8.von Kries R, Koletzko B, Sauerwald T, von Mutius E, Barnert D, Grunert V, von Voss H. Breastfeeding and obesity: cross sectional study. Brit Med J 1999;319:147-150
9. Toschke AM, Vignerova J, Lhotska L, Osancova K, Koletzko B, von Kries R. Overweight and obesity in 6- to 14- year-old Czech children in 1991: protective effect of breastfeeding. J Pediatrics 2002;141:764-769
10. Koletzko B, von-Kries R. Are there long term protective effects of breast feeding against later obesity? Nutr Health. 2001; 15: 225-36.
11. Arenz S, Rückerl R, Koletzko B, von Kries R. Breast-feeding and childhood obesity. A systematic review. Int J Obesity 2004;28:1247-1256
12. Mathew OP, Bhatia J. Sucking and breathing patterns during breast- and bottle-feeding in term neonates. Effects of nutrient delivery and composition. Am J Dis Child. 1989 May;143(5):588-92.
13. Bosma JF, Hepburn LG, Josell SD, Baker K. Ultrasound demonstration of tongue motions during suckle feeding. Dev Med Child Neurol. 1990 Mar;32(3):223-9.
14. Sievers E, Oldigs HD, Santer R, Schaub J. Feeding patterns in breast-fed and formula-fed infants. Ann Nutr Metab. 2002;46(6):243-8.
15. Agras WS, Kraemer HC, Berkowitz RI, Hammer LD. Influence of early feeding style on adiposity at 6 years of age. J Pediatr. 1990 May;116(5):805-9.
16. Mennella JA, Jagnow CP, Beauchamp GK. Prenatal and postnatal flavor learning by human infants. Pediatrics. 2001 Jun;107(6):E88.
17.Klaus M. Mother and infant: early emotional ties. Pediatrics. 1998 Nov;102(5 Suppl E):1244-6.
18. Mezzacappa ES.Breastfeeding and maternal stress response and health. Nutr Rev. 2004 Jul;62(7 Pt 1):261-8.
19. Kramer MS, Guo T, Platt RW, Vanilovich I, Sevkovskaya Z, Dzikovich I, Michaelsen KF, Dewey K; Promotion of Breastfeeding Intervention Trials Study Group. Feeding effects on growth during infancy. J Pediatr. 2004 Nov;145(5):600-5.
20. Dewey KG. Growth characteristics of breast-fed compared to formula-fed infants. Biol Neonate. 1998;74(2):94-105.
21. 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 May;158(5):449-52.
22. Heinig MJ, Nommsen LA, Peerson JM, Lonnerdal B, Dewey KG. Energy and protein intakes of breast-fed and formula-fed infants during the first year of life and their association with growth velocity: the DARLING Study. Am J Clin Nutr. 1993 Aug;58(2):152-61.
23. Alexy U, Kersting M, Sichert-Hellert W, Manz F, Schöch G. Macronutrient intake of 3- to 36-month-old German infants and children: results of the DONALD Study. Dortmund Nutritional and Anthropometric Longitudinally Designed Study. Ann Nutr Metab. 1999;43(1):14-22.
24. Daenzer M, Ortmann S, Klaus S, Metges CC.Prenatal high protein exposure decreases energy expenditure and increases adiposity in young rats. J Nutr. 2002 Feb;132(2):142-4.

25. Kim S, Mauron J, Gleason R, Wurtman R. Selection of carbohydrate to protein ratio and correlations with weight gain and body fat in rats allowed three dietary choices. Internat J Vit Nutr Res 1991;61:166-179.
26. Jones A, Simson E, Friedman M. Gestational undernutrition and the development of obesity in rats. Journal of Nutrition 1984;114:1484-92.
27. Lucas A, Boyes S, Bloom SR, Aynsley-Green A. Metabolic and endocrine responses to a milk feed in six-day-old term infants: differences between breast and cow's milk formula feeding. Acta Paediatr Scand. 1981 Mar;70(2):195-200.
28. Karlberg J, Jalil F, Lam B, Low L, Yeung CY. Linear growth retardation in relation to the three phases of growth. Eur J Clin Nutr. 1994;48(Suppl 1):S25-S43.
29. Hauner H, Wabitsch M, Zwiauer K, Widhalm K, Pfeiffer EF. Adipogenic activity in sera from obese children before and after weight reduction. Am J Clin Nutr 1989;50(1):63-7.
30. Rolland-Cachera MF, Deheeger M, Akrout M, Bellisle F. Influence of macronutrients on adiposity development: a follow-up study of nutrition and growth from 10 months to 8 years of age. Int J Obes Metab Disord 1995;19(8):573-8.
31. Scaglioni S, Agostoni C, DeNotaris R, et al. Early macronutrient intake and overweight at five years of age. Int J Obesity 2000;24.
32. Parizkova J, Rolland-Cachera M. High proteins early in life as a predisposition for later obesity and further health risks. Nutrition 1997;13:818-9.
33. Akeston PMK, Axelsson IEM, Raiha NCR. Growth and nutrient intake in three to twelve month old infants fed human milk or formulas with varying protein concentrations. Journal of Pediatric Gastroenterology and Nutrition 1998;26:1-8.