www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2013;2(2):e020206
doi: 10.7363/020206 Received: 2013 Jun 05; accepted: 2013 Jul 29; advance publication: 2013 Aug 10

Review

Breastfeeding reduces the risk of obesity in childhood and adolescence

Eleni-Maria Papatesta, Nicoletta Iacovidou

National and Kapodistrian University of Athens, Medical School, 2nd Department of Obstetrics and Gynecology, Neonatal Division, Aretaieio Hospital, Athens, Greece

Abstract

Childhood obesity has increased dramatically over the last decades, representing one of the most serious public health hazards of the 21st century. Efforts must be made by healthcare professionals to prevent it, as it is associated with short- and long-term risks for physical and mental health and because of the increased possibility to persist during adulthood. From antiquity human breast milk was considered the ideal nourishment for the newborn. Breastfeeding is beneficial for the mother-child dyad. Among others, existing data suggest that it reduces the risk for childhood and adolescence obesity. The mechanisms for this are numerous and include the feeding behavior breastfeeding infants acquire, their growth rate, the 'early protein hypothesis', the role of leptin that is found in increased levels in human milk, the dietary choices the breastfed infants make during childhood and adolescence and finally the differences in their bowel flora. Meta-analyses provide sufficient evidence for this protective effect, with a dose-response effect as to the duration of breastfeeding. Healthcare professionals involved in the care of the mother-infant dyad must encourage and support mothers to breastfeed their infants for a long period of time, if obesity were to be prevented. Aim of this review is to provide an account of existing data on the association of breastfeeding and the reduced risk of obesity in childhood and adulthood.

Keywords

Breastfeeding, obesity, childhood, adolescence.

Corresponding author

Dr Nicoletta Iacovidou, 3, Pavlou Mela St, 16233 Athens, Greece; tel.: +30 2107641281; fax: +30 2107233330; e-mail addresses: niciac58@gmail.com, niciac@otenet.gr.

How to cite

Papatesta E-M, Iacovidou N. Breastfeeding reduces the risk of obesity in childhood and adolescence. J Pediatr Neonat Individual Med. 2013;2(2):e020206. doi: 10.7363/020206.

Historical data on breastfeeding

From antiquity human breast milk was considered to be the newborn's ideal nourishment. In ancient Egypt, in ancient Greece and in the Roman time babies were breastfed for long. The Romans thought that the semen and the mother's milk influenced the physical appearance and the character of the newborn. However, women from wealthy families or from the upper social class, or those incapable to breastfeed, used to employ the so-called 'wet nurses' to breastfeed their children. These women were wet nurses by profession and had to be healthy and of moral integrity.

In the Byzantine time though, according to Aetios and Oribasios, the newborn's first nutrition was honey, since they believed that colostrum was inappropriate food and breastfeeding should begin after the third day of life. Wet nurses were also employed during this period, even though Church was against this practice.

Breastfeeding is presented in mythology of various civilizations as well. Zeus, the Father of Greek Gods was breastfed by the goat Amalthea; Romulus and Remus, the founders of Rome, were breastfed by a wolf.

Breastfeeding, as a practice, has been the theme of inspiration for many artists. Isis, the Egyptian goddess, is shown in a sculpture breastfeeding her son Horus. Maria Lactans paintings, i.e. Virgin Mary Nursing, were very popular especially in the 12th through the 14th centuries. The Spanish painter Pablo Picasso created 2 magnificent paintings, spaced apart by almost 60 years, of a mother breastfeeding her child.

Breastfeeding was widespread until late in the 19th century; it then started to decline in the Western world, when commercial infant formula was manufactured, which soon became very popular and widely used. After a period of abandonment of breastfeeding for social reasons mainly, there was a resurgence of breastfeeding in the early 1960s, since the benefits of breastfeeding for the mother and child begun to be recognized by the scientific community worldwide. Since then, International Organizations like WHO and UNICEF have launched campaigns in an effort to spread widely breastfeeding through the increase of the awareness of its value. Maternal milk not only provides an ideal nutrition for the newborn but it represents the final part of the reproductive process [1-4].

Introduction

Breastfeeding is beneficial both for the child and the mother. Regarding the infant it is documented that it reduces the risk of infections such as acute otitis media, non-specific gastroenteritis and severe lower respiratory tract infections, but also the risk of atopic dermatitis, asthma, obesity, type 1 and 2 diabetes, childhood leukemia, sudden infant death syndrome (SIDS) and necrotizing enterocolitis [5]. In addition breastfeeding is associated with better cognitive development during childhood, and lower mean blood pressure and lower total cholesterol in adulthood [6].

Regarding the mother, breastfeeding has been associated with reduced risk of breast and ovarian cancer and of maternal type 2 diabetes [5].

Over the last decades the frequency of childhood obesity has risen dramatically and has become one of the most serious public health concerns of the 21st century. It is estimated that in 2010 more than 40,000,000 children aged less than 5 years old were obese worldwide [7]. Obesity is defined as *abnormal or excessive fat accumulation in the body that may impair health* [8]. Body Mass Index (BMI) is used in order to estimate obesity in children 2 years of age and older and adolescents. This is defined as a person's weight in kilograms divided by the square of his/hers height in meters (kg/m^2). Growth Charts are used for children and adolescents (2-19 years old) to determine the matching BMI for age and gender percentile. Overweight children are those with a BMI for age and gender greater than the 85th and lower than the 95th centile. Obese children are those with a BMI for age and gender greater than the 95th centile [9].

Childhood obesity must be prevented because it is associated with an increased risk for cardiovascular disease (high blood pressure and dyslipidemia) [10], for coronary heart disease and metabolic syndrome [11, 12], for fatty liver disease [13], for hyperinsulinemia and insulin resistance and type 2 diabetes [14, 15]. Furthermore it is associated with increased risk for respiratory complications such as obstructive sleep apnea [16]

and asthma [17], increased frequency of fractures and musculoskeletal distress [18] and psychosocial consequences because of the discrimination and limitations that obese children and adolescents experience in everyday life [19-21].

In this review we aim at examining existing data in the literature supporting the protective role of breastfeeding against the risk of obesity in childhood and adolescence.

Possible mechanisms for the protective role of breastfeeding against the risk of obesity in childhood and adolescence

Several studies suggest that breastfeeding is associated with a lower risk of obesity and several meta-analyses prove this positive association. The question, though, that must be answered is by which mechanism breastfeeding exerts this protective effect on childhood obesity. Many hypotheses have been made, however none has been completely proven so far.

Feeding behavior

There are differences between the feeding behavior of breastfed infants and of those who do not breastfeed. Infants who breastfeed have a higher control of their food intake and they develop self-regulation of energy intake [22]. They control the quantity, duration and frequency of their meals based on their feeling of hunger and satiation. Infants who are formula-fed tend to empty the bottle and usually the parents are those who decide on the amount of milk to be consumed, encouraging their infants to empty the bottle. Sievers et al. reported that 6-week old formula-bottled fed babies consumed 20-30% higher volume than breastfed babies and had less frequent meals [23]. Infants who are bottle-fed early in life are 2 times more likely to consume the whole quantity of the offered meal in later infancy [24]. Breastfeeding during early infancy is also associated with greater appetite regulation later in childhood when compared to that of bottle-fed infants [25].

Growth rate

Increased weight gain early in life is associated with obesity later in life. Rapid weight gain during the first 4 months of life was correlated with a higher risk of overweight at the age of 7 years, independent of birth weight and weight at the age of 1 year. Stettler and co-workers estimated that 20% of the risk of obesity at age 7 years could be attributed to a rate of weight gain in the top quintile in the first 4 months of life [26].

Breastfed infants have a lower rate of weight gain, which is different from the one in infants who do not breastfeed. Formula milk compared to breast milk has a growth-accelerating influence on infants. [27, 28]. The difference in body weight is about 400 g and 600-650 g in infants breastfed for 9 and 12 months respectively at the age of 12 months old [29].

The early protein hypothesis

High protein intake in formula-fed infants seems to be associated with increased risk of obesity through increased adipogenic activity and adipocyte differentiation. It may also decrease human growth hormone (hGH) secretion and lipolysis [30]. In a multicenter European study, formula-fed babies were randomized to receive formula with lower or higher protein content for the first year of life and were compared with babies that breastfed exclusively. Infants in the lower protein formula group presented lower weight-for length z score than that of the higher protein group and similar weight-for length z score with the breastfed reference group [31].

High protein intake early in life is positively associated with higher BMI during childhood and negatively associated with the age of adiposity rebound, adjusted for parental BMI [32, 33]. Heinig et al. reported that during the first 6 months of life the protein intake was 66-70% higher in infants of the formula-fed group than that in the breastfeeding group. The latter presented lower lean body mass and weight gain than infants in the formula-fed group from 3-9 months [34].

High protein intake is positively related with the risk of overweight and this may occur *via* the stimulation of insulin secretion. High protein supply leads to an augmentation in the circulation of insulin stimulating amino-acids [35]. Formula-fed infants had higher postprandial plasma insulin levels and prolonged insulin response on day 6 of life compared to breastfed infants [36]. Higher insulin levels stimulate increased adipose tissue deposition increasing thus the risk of weight gain, obesity, and type 2 diabetes [37]. Moreover, high insulin like growth factor (IGF-I) concentrations in infancy were associated with obesity later in

life. Lack of breastfeeding, and therefore formula feeding are related with higher serum IGF-1 concentrations compared to breastfed infants (at 6 and 9 months of life) [38, 39].

The role of leptin

Besides insulin, leptin seems to play a significant role in the protective role of breastfeeding against obesity. Leptin inhibits appetite and controls energy metabolism. Breast milk contains leptin whereas formula milk does not. Breast milk leptin concentration correlates positively with maternal plasma leptin concentration and with maternal BMI. The milk concentration of leptin during the first phases of lactation (1 month) may affect the infant's body weight of non-obese mothers at 12 and 24 months of age [40].

In addition, early diet of preterm infants is related to leptin concentrations at 13-16 years old. Infants who had a higher intake of human milk presented significantly lower leptin concentrations relative to fat mass in adolescence, after adjusting for potential confounding factors (age, sex, fat mass). This indicates that early feeding mode may influence later obesity [41].

Dietary choices in childhood and adolescence

Early feeding mode may affect later dietary choices. Unlike formula milk, the human breast milk presents a significant variety in nutrient content, taste and smell daily, depending on factors such as maternal diet, duration of lactation and the degree of breast expression [42]. Early postnatal exposure to a flavor, encourages the infant's acceptance and thus consumption of the same flavor [43]. Since a breastfeeding infant is exposed to a variety of flavors and smells, it is likely that it is programmed to a different food selection and to different dietary habits later in life. This link between breastfeeding and later dietary habits is also presented in a study by Burnier et al. showing that exclusive breastfeeding for at least 3 months, is a prognostic factor of higher consumption of vegetables in preschool children [44].

Hyh et al. compared breastfed and formula-fed infants and reported that the introduction of solid foods before the age of 4 months is associated with a 6-fold increase in the likelihood of obesity at the age of 3 years, only for the formula fed infants. No such an association was detected in breastfed babies [45].

Bowel flora

Differences in intestinal flora composition were reported to be related with an increased risk of obesity [46]. Breastfed infants have different gut microflora compared to that of formula-fed infants, which is characterized by a larger abundance of species of greater diversity [47, 48]. It seems that these differences in gut microflora are associated with certain diseases including obesity, but more research must be done. According to Kalliomaki et al., the possible link between breastfeeding and weight progress is the presence or not of bifidobacteria. Children of normal weight at the age of 7 years old, had a higher number of bifidobacteria than those who were overweight. Also, it has been shown that breast milk contains bifidobacteria, which consist the typical gut microflora of healthy breastfed infants [49].

Clinical studies on the protective role of breastfeeding against the risk of obesity in childhood and adolescence

Arenz et al. in a meta-analysis in 2004 examined the relationship between breastfeeding and childhood obesity. Nine of the 28 studies reviewed met the eligibility criteria and were included in the study (n = 69,000). The meta-analysis showed that breastfeeding reduced the risk of childhood obesity significantly. In 4 studies a dose-dependent effect of the duration of breastfeeding on the prevalence of obesity was reported [50].

Harder et al., in 2005, attempted to link the duration of breastfeeding and the risk of overweight. Seventeen studies were included in the meta-analysis (n = 120,831) comparing breastfed infants *versus* exclusively formula-fed infants, where the duration of breastfeeding was reported. The duration of breastfeeding was inversely related with the risk of overweight. In addition, a dose-response effect was reported. It was also shown that with each additional month of breastfeeding up to 9 months, the odds of overweight were reduced by 4% [51].

Owen et al., in 2005, investigated the influence of initial infant feeding on obesity later in life. Twenty-eight studies were included (n = 298,900). Breastfeeding was reported to be associated with a reduced risk of obesity, compared with formula feeding. In 6 studies that adjusted for 3 confounding factors – socioeconomic status,

parental BMI, maternal smoking – the inverse association remained but it was reduced from 0.86 (95% CI = 0.81, 0.91) to 0.93 (95% CI = 0.88, 0.99). Four studies that included exclusively initial breastfeeding groups showed a stronger protective effect compared with all other studies (OR = 0.76, 95% CI = 0.70, 0.83). Longer duration of breastfeeding also exhibited a greater protective effect on obesity. The protective effect of breastfeeding compared to formula feeding was greater among infants breastfed for at least 2 months, compared with those breastfed for any duration in the same studies [52].

In the AHQR report, the effects of breastfeeding on short- and long- term infant and maternal health outcomes in developed countries were examined. Breastfeeding was associated with a reduction in the risk of obesity [5].

Children, who did not breastfeed compared to those who did, presented a 32% excess risk of childhood obesity [53].

Finally, in a meta-analysis conducted by Horta et al., in 2007, 33 studies were included. Breastfed infants were less probable to be considered as overweight/obese. The protective effect of breastfeeding remained among small studies (< 500 participants), studies with 500-1,500 participants and studies with more than > 1,500 participants although it was higher among small studies [6].

The results of the above mentioned studies may be due to confounding factors that haven't been measured. Furthermore, these studies are based on observation and cannot prove causality.

Mothers who breastfeed, follow a healthier lifestyle, have healthier dietary habits and increased physical activity for them and their children. We are in need of randomized clinical trials but we cannot randomize infants in breastfeeding and non-breastfeeding group for ethical reasons and because of the known effects of breastfeeding for the infant's well-being [54].

Metzger et al. investigated the relationship between infant feeding and BMI in late childhood or adolescence. They enrolled siblings whom only one of the two was breastfed. The breastfed sibling had lower BMI during adolescence, equivalent to a difference greater than 13 pounds (6 kg) for a child of 14 years, of average height. In addition breastfed siblings were less likely to reach dangerous levels of obesity BMI [55].

Crume et al. investigated the role of breastfeeding on body mass index (BMI) growth trajectory, from birth through 13 years of age among children of diabetic pregnancies and children of non-diabetic pregnancies. Breastfeeding was related with lower BMI growth trajectories during childhood in both groups. Thus, the positive influence of breastfeeding remains for the high-risk infants (infants of diabetic pregnancies who are exposed to over nutrition during pregnancy) [56].

Shorter duration of breastfeeding was associated with higher peripheral and total subcutaneous fat mass at the age of 6 months. Infants who were non-exclusively breastfed had a higher central fat mass at the age of 24 months [57].

Childhood obesity must be prevented, as obese children are more likely to become obese adults. One third of obese preschool children developed obesity in adulthood, and about half of obese school-age children became obese adults [58].

In a more recent study, almost two third of the participants who were in the highest BMI quartile in childhood, remained in the highest BMI quartile in young adulthood [59].

Obesity and metabolomics

Obesity is a multifactorial disease but we don't know in details the mechanisms by which genetic background, dietary habits and environment may interact with each other. New techniques need to be applied in the research of this global disease. Metabolomics, i.e. the study of small molecule metabolites in biological samples, is one of these techniques and they may contribute greatly not only in the understanding of these mechanisms but they may help to detect biomarkers associated with it. Until now, several metabolites that are associated with obesity have been identified in human (adults and pediatric obese individuals) and animal models. Metabolites related to glucose metabolism such as lactate, related to lipid metabolism such as free fatty acids, branched chain amino acids (BCAAs), leucine, isoleucine, and valine but also polyamines (putrescine, spermidine, and spermine) which are correlated to markers of oxidative-nitrosative stress and angiogenesis, seem to be associated with obesity. These biomarkers could serve as diagnostic tools in a personalized healthcare setting and could also serve as an alarming finding for prediction, prevention or treatment of the entity. In this respect, breastfeeding in combination with metabolomics analysis could be a weapon in disease prevention from early days in life [60-62].

Conclusions

In conclusion, sufficient evidence exists to support the protective effect of breastfeeding on the risk of obesity in childhood with a dose-response effect. Healthcare professionals involved in the care of the mother-infant dyad must encourage mothers to breastfeed their infants for a long period of time, if obesity were to be prevented. The protective effect of breastfeeding seems to remain not only during childhood, but also during adolescence and perhaps during adulthood. Prevention of obesity in general is of great importance and reduces the burden of its complications that is put on healthcare systems.

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. WHO. Breastfeeding. http://www.who.int/topics/breastfeeding/en/, last access: April 2013.
2. Testa M, Tsotra K. History of Breastfeeding. In: Fanos V, Yurdakök M (Eds.). Children of the Mother Goddess. History of Mediterranean Neonates. Quartu Sant'Elena: Hygeia Press, 2010.
3. Koutousi Ch, Kostoudi S, Myronidou-Tsouveleki M. The importance of breast-feeding and the history of feeding bottles. Pharmacology Lab, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece. Paediatr N Gr. 2005;17:19-30.
4. Moros M. [History and Philosophy of Breastfeeding: from antiquity to our days]. [Article in Greek]. "ELEFTHO". 2010;1:28-32.
5. Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, Trikalinos T, Lau J. Breastfeeding and maternal and infant health outcomes in developed countries. Evid Rep Technol Assess. 2007;153:1-186.
6. Horta BL, Bahl R, Martinés JC, Victora CG. Evidence on the long-term effects of breastfeeding: systematic review and meta-analyses. Geneva: World Health Organization, 2007.
7. WHO. Childhood overweight and obesity. http://www.who.int/dietphysicalactivity/childhood/en/, last access: April 2013.
8. WHO. Obesity and overweight. http://www.who.int/mediacentre/factsheets/fs311/en/index.html, last access: April 2013.
9. Centers for Disease Control and Prevention. Basics About Childhood Obesity. http://www.cdc.gov/obesity/childhood/basics.html, last access: April 2013.
10. Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. Pediatrics. 1999;103: 1175-82.
11. Owen CG, Whincup PH, Orfei L, Chou QA, Rudnicka AR, Wathern AK, Kaye SJ, Eriksson JG, Osmond C, Cook DG. Is body mass index before middle age related to coronary heart disease risk in later life? Evidence from observational studies. Int J Obes (Lond). 2009;33(8):866.
12. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, Allen K, Lopes M, Savoye M, Morrison J, Sherwin RS, Caprio S 2004 Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 350:2362-74.
13. Lavine JE, Schwimmer JB. Nonalcoholic fatty liver disease in the pediatric population. Clin Liver Dis. 2004;8:549-58.
14. Steinberger J, Moran A, Hong CP, Jacobs DR, Jr, Sinaiko AR. Adiposity in childhood predicts insulin resistance and obesity in young adulthood. J Pediatr. 2001;138:469-73.
15. Hannon TS, Rao G, Arslanian SA. Childhood obesity and type 2 diabetes mellitus. Pediatrics. 2005;116(2):473-80.
16. Mallory GB Jr, Fiser DH, Jackson R. Sleep-associated breathing disorders in morbidly obese children and adolescents. J Pediatr. 1989;115:892-7.
17. Sutherland ER. Obesity and asthma. Immunol Allergy Clin North Am. 2008;28(3):589-602.
18. Taylor ED, Theim KR, Mirch MC, Ghorbani S, Tanofsky-Kraff M, Adler-Wailes DC, Brady S, Reynolds JC, Calis KA, Yanovski JA. Orthopedic complications of overweight in children and adolescents. Pediatrics. 2006;117(6):2167-74.
19. Swartz MB, Puhl R. Childhood obesity: a societal problem to solve. Obesity Reviews. 2003;4(1):57-71.
20. Daniels SR. The consequences of childhood overweight and obesity. Future Child. 2006;16(1):47-67.
21. Han JC, Lawlor DA, Kimm SY. Childhood obesity. Lancet. 2010;375:1737-48.
22. Dewey KG, Lonnerdal B. Infant self-regulation of breast milk intake. Acta Paediatr Scand. 1986;75:893-8.
23. Sievers E, Oldigs HD, Santer R, Schaub J. Feeding patterns in breastfed and formula-fed infants. Ann Nutr Metab. 2002;46:243-8.
24. Li R, Fein SB, Grummer-Strawn LM. Do Infants Fed From Bottles Lack Self-regulation of Milk Intake Compared With Directly Breastfed Infants? Pediatrics. 2010;125:e1386.
25. Disantis KI, Collins BN, Fisher JO, Davey A. Do infants fed directly from the breast have improved appetite regulation and slower growth during early childhood compared with infants fed from a bottle? Int J Behav Nutr Phys Act. 2011;8:89.
26. Stettler N, Zemel BS, Kumanyika S, StallingsVA. Infant weight gain and childhood overweight status in a multicenter, cohort study. Pediatrics. 2002;109:194-9.
27. Ong KK, Loos RJ. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. Acta Paediatr. 2006;95(8):904-8.
28. Kramer MS, Guo T, Platt RW, Vanilovich I, Sevkovskaya Z, Dzikovich I, Michaelsen KF, Dewey K. Feeding effects on growth during infancy. J Pediatr. 2004;145:600-5.
29. Dewey KG. Growth characteristics of breast-fed compared to formula-fed infants. Biol Neonate. 1998;74(2):94-105.
30. Koletzko B, Broekaert I, Demmelmair H, Franke J, Hannibal I, Oberle D, Schiess S, Baumann BT, Verwied-Jorky S; EU Childhood Obesity Project. Protein intake in the first year of life: a risk factor for

later obesity? The E.U. childhood obesity project. In: Koletzko B, Dodds PF, Akerblom H, Ashwell M (Eds.). Early nutrition and its later consequences: new opportunities. New York: Springer Publishers, 2005.

31. Koletzko B, von Kries R, Closa R, Escribano J, Scaglioni S, Giovannini M, Beyer J, Demmelmair H, Gruszfeld D, Dobrzanska A, Sengier A, Langhendries JP,Rolland Cachera MF, Grote V; European Childhood Obesity Trial Study Group. Lower protein in infant formula is associated with lower weight up to age 2 y: a randomized clinical trial Am J Clin Nutr. 2009;89(6):1836-45.
32. 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 Relat Metab Disord. 1995;19:573-8.
33. Scaglioni S, Agostoni C, Notaris RD, Radaelli G, Radice N, Valenti M, Giovannini M, Riva E. Early macronutrient intake and overweight at five years of age. Int J Obes Relat Metab Disord. 2000;24(6):777-81.
34. 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;58:152-61.
35. Axelsson IE, Ivarsson SA, Raiha NCR. Protein intake in early infancy: effects on plasma amino acid concentrations, insulin metab- olism and growth. Pediatr Res. 1989:26:614-7.
36. Lucas A, Boyes S, Bloom R, 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;70:195-200.
37. Odeleye OE, de Courten M, Pettitt DJ, Ravussin E. Fasting hyperinsulinemia is a predictor of increased body weight gain and obesity in Pima Indian children. Diabetes. 1997;46:1341-5.
38. Socha P, Janas R, Dobrzañska A, Koletzko B, Broekaert I, Brasseur D, Sengier A, Giovannini M, Agostoni C, Monasterolo RC, Méndezs G; EU Childhood Obesity Study Team. Insulin like growth factor regulation of body mass in breastfed and milk formula fed infants. Data from the E.U. Childhood Obesity Programme. In: Koletzko B, Dodds PF, Akerblom H, Ashwell M (Eds.). Early nutrition and its later consequences: new opportunities. New York: Springer Publishers, 2005.
39. Madsen AL, Larnkjær A, Mølgaard C, Michaelsen KF. IGF-I and IGFBP-3 in healthy 9 month old infants from the SKOT cohort: breastfeeding, diet, and later obesity. Growth Horm IGF Res. 2011;21(4):199-204.
40. Miralles O, Sánchez J, Palou A, Picó C. A physiological role of breast milk leptin in body weight control in developing infants. Obesity. 2006;14:1371-7.
41. 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(6):993-9.
42. Rodriguez-Palmero M, Koletzko B, Kunz C, Jensen R. Nutritional and biochemical properties of human milk: II. Lipids, micronutrients, and bioactive factors. Clin Perinatol. 1999;26:335-59.
43. Mennella JA, Jagnow CP, Beauchamp GK. Prenatal and postnatal flavor learning by human infants. Pediatrics. 2001;107:E88.
44. Burnier D, Dubois L, Girard M. Exclusive breastfeeding duration and later intake of vegetables in preschool children Eur J Clin Nutr. 2011;65(2):196-202.
45. Huh SY, Rifas-Shiman SL, Taveras EM, Oken E, Gillman MW. Timing of solid food introduction and risk of obesity in preschool-aged children. Pediatrics. 2011;127:e544-51.
46. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006;444(7122):1022-3.
47. Bezirtzoglou E, Tsiotsias A, Welling GW. Microbiota profile in feces of breast- and formula-fed newborns by using fluorescence in situ hybridization (FISH). Anaerobe. 2011;17:478-82.
48. Azad MB, Konya T, Maughan H, Guttman DS, Field CJ, Chari RS, Sears MR, Becker AB, Scott JA, Kozyrskyj AL; CHILD Study Investigators. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. CMAJ. 2013;185(5):385-94.
49. Kalliomäki M, Collado MC, Salminen S, Isolauri E. Early differences in fecal microbiota composition in children may predict overweight. Am J Clin Nutr. 2008;87:534-8.
50. Arenz S, Ruckerl R, Koletzko B, von Kries R. Breastfeeding and childhood obesity: a systematic review. Int J Obes Relat Metab Disord. 2004;28:1247-56.
51. Harder T, Bergmann R, Kallischnigg G, Plagemann A. Duration of breastfeeding and risk of overweight: a meta-analysis. Am J Epidemiol. 2005;162:397-403.
52. Owen CG, Martin RM, Whincup PH, Smith GD, Cook DG. Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence. Pediatrics. 2005;115:1367-77.
53. U.S. Department of Health and Human Services. The Surgeon General's Call to Action to Support Breastfeeding. Washington, DC: U.S. Department of Health and Human Services, Office of the Surgeon General, 2011.
54. Division of Nutrition and Physical Activity. Research to Practice Series No. 4: Does breastfeeding reduce the risk of pediatric overweight? Atlanta: Centers for Disease Control and Prevention, 2007.
55. Metzger MW, McDade TW. Breastfeeding as obesity prevention in the United States: a sibling difference model. Am J Hum Biol. 2010;22(3):291-6.
56. Crume TL, Ogden LG, Mayer-Davis EJ, Hamman RF, Norris JM, Bischoff KJ, McDuffie R, Dabelea D. The impact of neonatal breast-feeding on growth trajectories of youth exposed and unexposed to diabetes in utero: The EPOCH study. Int J Obes (Lond). 2012;36:529-34.
57. Durmuş B, Ay L, Duijts L, Moll HA, Hokken-Koelega AC, Raat H, Hofman A, Steegers EA, Jaddoe VW. Infant diet and subcutaneous fat mass in early childhood: the Generation R Study. Eur J Clin Nutr. 2012;66(2):253-60.

58. Serdula MK, Ivery D, Coates RJ, Freedman DS. Williamson DF. Byers T. Do obese children become obese adults? A review of the literature. Prev Med. 1993;22:167-77.
59. Deshmukh-Taskar P, Nicklas TA, Morales M, Yang SJ, Zakeri I, Berenson GS. Tracking of overweight status from childhood to young adulthood: the Bogalusa Heart Study. Eur J Clin Nutr. 2006;60:48-57.
60. Zhang A, Sun H, Wang X. Power of metabolomics in biomarker discovery and mining mechanisms of obesity. Obes Rev. 2013;14(4):344-9.
61. Codoner-Franch P, Tavarez-Alonso S, Murria-Estal R, Herrera-Martin G, Alonso-Iglesias E. Polyamines Are Increased in Obese Children and Are Related to Markers of Oxidative/ Nitrosative Stress and Angiogenesis. J Clin Endocrinol Metab. 2011;96:2821-5.
62. Xie B, Waters MJ, Schirra HJ. Investigating potential mechanisms of obesity by metabolomics. J Biomed Biotechnol. 2012;2012:805683.