*Koletzko B. Childhood obesity: current situation and future opportunities. J Pediatr Gastro Nutr 2016 Jul;63 Suppl 1:S18-21. doi: 10.1097/MPG.0000000000001220*

**Title:**

**Childhood obesity: current situation and future opportunities**

**Author:** Berthold Koletzko

**Author's affiliation:** Ludwig-Maximilians-Universität München, Dr. von Hauner Children's Hospital, University of Munich Medical Center, Munich, Germany

**Correspondence:** Berthold Koletzko, Univ.-Prof. Dr. Dr., Ludwig-Maximilians-Universität München, Dr. von Hauner Children's Hospital, Klinikum der Universität München, Lindwurmstr. 4, 80337 München, Germany. Phone: +49 89 44005 2826, Email: office.koletzko@med.lmu.de

**Abstract** *(198 words)*

*Purpose of review:* The early origins of overweight and obesity and the opportunities for early prevention are explored.

*Recent findings:* Overweight and obesity prevalence globally has increased at an alarming rate. No single intervention can halt the rise of the obesity epidemic. Particular attention is given to exploring causative factors and preventive measures in early life, when biological determinants of risk trajectories, feeding behaviour and dietary preferences are shaped. Some lifestyle and nutrition modifications in pregnancy and infancy can reduce subsequent obesity risk. Also postnatal infant gut colonisation may modify later obesity risk, but currently available evidence does not allow firm conclusions. Surprisingly, about 3.2 times more systematic reviews (SR) than randomized clinical trials (RCTs) were published on "probiotics" and health, and even 7.9 times more SR than RCTs on "probiotics" and obesity, which is not helpful.

*Summary:* Multiple research opportunities exist for exploring the early origins of obesity to contribute towards halting the rise in obesity prevalence. Exploring the early development of the microbiome in its complexity, its dependence on dietary and other exogenous factors, and its metabolic and regulatory functions is promising. Meaningful progress for obesity prevention can most likely be achieved by combining several strategies.

**Keywords:** Probiotics, microbiome, childhood obesity, early metabolic programming of health, developmental origins of adult health and disease

**Abbreviation:** BMI = body mass index

*Koletzko B. Childhood obesity: current situation and future opportunities. J Pediatr Gastro Nutr 2016 Jul;63 Suppl 1:S18-21. doi: 10.1097/MPG.0000000000001220*

*Text 1765 words*

## Introduction

Since the 1980ies, an alarming increase in the prevalence of overweight and obesity has occurred among adults, adolescents and children globally, not only in high income countries, but also in low and medium income countries around the world (1). This has resulted in major and global health challenges, because overweight and particularly obesity are associated with severe health consequences. These include insulin resistance, metabolic syndrome and diabetes mellitus, as well as other non-communicable diseases including hypertension, dyslipidemia, stroke and ischemic heart disease, steatohepatitis, musculocelatal and orthopedic disordes, gout, social stigmatisation, mental health problems, and some forms of cancer. The resulting burdens of disease and the health economic consequences are huge. The loss of total life years and of healthy life years, respectively, due to overweight and obesity at the age of 20 to 39 years has been estimated from data of almost 4000 participants of the U.S. National Nutrition and Examination Survey (2). Overweight leads to the loss of ≈6 healthy life years, while severe obesity with a BMI <35 causes the loss of ≈19 healthy life years (Fig. 1). It is estimated that in the European Union alone, obesity causes some 2.8 million premature deaths per year, and 7% of the health care expenses are spent for obesity and its consequences, with a rapidly increasing trend (3). The cost attributed only to diabetes as one of the main consequences of obesity have been estimated as € 2 391 per patient and year in Germany, of which 26.5% arise for costs of hyperglycaemia management and 73.5% (€ 1 758) for costs of the treatment of complications (4).

While most of the consequences of obesity become apparent in adulthood, the underlying pathogenic process begins early in life. An estimated 42 million children worldwide are overweight or obese (5). In the European Union, already one in three children aged 6 to 9 years is overweight or obese (3). Most of these children will remain in the same or even higher BMI category during their adult life, resulting in significantly higher lifetime costs as compared to normal weight children (6). Therefore, obesity must be addressed already early in life. However, current approaches towards effective treatment and prevention of childhood obesity remain far less than satisfactory (7, 8). Hence, obesity prevalence continues to increase in many populations around the world.

In their recent report, the Commission on Ending Childhood Obesity of the World Health Organisation concluded that no single intervention can halt the rise of the obesity epidemic (5). The Commission recommended that particular attention should be devoted to preventive measures in three sensitive periods of the life course, i.e. preconception and pregnancy, infancy and early childhood, and older childhood and adolescence. Similarly, a report of the U.S. Institute of Medicine concluded that efforts to prevent childhood obesity must begin before children enter the school system (9). The early periods of life offer particular opportunities at a time when biological determinants of risk trajectories, feeding behaviour and dietary preferences are shaped. This is exemplified by recently published data from the Early Childhood Longitudinal Study in 7738 children in the USA. The annual incidence of obesity was highest at the Kindergarten age with 5.4% and fell to 1.7% per year between the fifth and eight grades of school (10). Incident obesity up to the age of 14 years was 4 times higher if children were overweight by the age of 5 years, as compared to normal weight during pre-school age. A high birthweight >4 kg, as compared to a lower birthweight, induced a 5,1fold higher risk of becoming overweight by the eighth school grade (10).

**Early programming of the later obesity risk**

Early lifestyle and nutrition during the period of marked developmental plasticity in the first about 1000 days of life (270 days of pregnancy and 2 times 365 days of the first two postnatal years) induces marked programming effects on long-term health until old age, including the risks of adiposity, obesity and associated disorders such as diabetes (11, 12). Early environmental cues, including nutrition, modulate cytogenesis, organogenesis, metabolic and endocrine response, pre- and postnatal growth trajectories, and the epigenetic regulation of gene expression (Fig. 2). Current research on early prevention of obesity risk focusses on three key hypotheses of early nutrition programming of later obesity and increased body fat content (adiposity) (13, 14). The "*Fuel mediated in utero Hypothesis*" stipulates that fetal exposure to an excess of fuels (e.g. glucose, fatty acids), that can result from maternal obesity or diabetes, enhances fetal weight and body fat gain and leads to increased obesity and associated non-communicable diseases (NCD) later in life. The "*Accelerated Postnatal Growth Hypothesis*" links rapid weight gain in infancy and early childhood to an increased risk of later obesity and other NCD. The "*Mismatch Hypothesis*" describes that a mismatch of low prenatal weight gain and low birthweight, along with high postnatal weight gain, markedly increases later disease risk (11).

Considerable evidence now supports these three hypotheses. Maternal obesity has been linked to increased infant birthweight and body fat content, increased later obesity risk, and significantly shorter life expectancy of the child. Prevention appears possible. For example, in the randomized controlled LIMIT trial, three face to face sessions counselling overweight women during pregnancy to encourage regular physical activity and to limit the dietary intake of sugars and dietary fat achieved a significant reduction of high infant birthweight >4 kg by 19% (15). This is considered a major benefit, since a birthweight > 4kg was shown to increase obesity risk in adulthood about twofold (16). Numerous studies also link high weight gain in infancy and in the second year of life to an approximately doubled risk of obesity up to adulthood (17). Breastfeeding reduces the likelihood of both high early weight gain and later obesity (18). Several meta-analyses of large cohort studies reveal that breast feeding reduces the risk of later by about 12-24%, compared to conventional bottle feeds (19-21). The risks for later obesity linked with formula-feeding can be attenuated by improving the composition of infant formula. In a large multicentric, randomized double-blind clinical trial funded by the European Commission, we demonstrated that feeding formulae with a lesser protein content, more similar to the protein content of human milk, normalizes early weight gain relative to breastfed infants, and it markedly reduces obesity risk at school age 2.4-2.9 fold (22, 23). Further opportunities exist during the complementary feeding period by avoiding overfeeding as well as excessive intakes of sugar and dairy protein (24).

**Early modification of the microbiome as a means for reducing obesity risk?**

The postnatal colonisation of the infant gut with bacteria begins immediately after birth and matures until about two years of age. Early exposure to different bacteria, dietary composition, birth by caesarean section, treatment with antibiotics and other factors can have lasting effects on this colonisation of the gut and potential biological and health consequences. Studies in rodents demonstrated a marked influence of gut bacteria on body weight development and body fat deposition pointing towards a great potential of modifying obesity risk through supporting a protective microbiome. However, direct extrapolation of such rodent data to humans is inappropriate, in particular because the degree of scavenging energy from unabsorbed nutrients entering the colon for systemic use appears to be far greater in rodents than in humans on current Western diets. However, also observational studies in humans associated e.g. caesarean section and bacterial composition of stools with growth and body size (25). While data from

experimental models and observations in epidemiological studies contribute markedly to our scientific understanding, they do not suffice for drawing conclusions on causality and on benefits of interventions in humans. Controlled intervention studies of high quality and with adequate power are required to devise recommendations on policy and practice. But so far only few randomized and non-randomized studies have been published, with some methodological issues, which however provide some indications that the administration of certain bacteria (encapsulated or provided in the form of fermented yoghurt) might be beneficial for reducing body weight or body fat either in the recipient subjects, or in their offspring (26).

The lack of consistent and fully convincing evidence in humans is sometimes overlooked due to the truly amazing plethora of systematic reviews that have been published in this area. A simple search in the PubMed database of the U.S. National Library of Medicine performed on 8 March 2016 using the search terms "probiotic* AND health"or "probiotic* AND obesity" combined with either "randomized clinical trial"or "systematic review" revealed 3.2 times as many systematic reviews (SRs) than original randomized trials (RCTs) on "health", and even 7.9 times as many SRs than RCTs on "obesity" (Table 1). This is clearly inadequate and appears to reflect the widespread rather uncritical confidence in systematic reviews as the source of definite answers to pertinent questions, without critically analysing the limitations and heterogeneity of the studies on which such reviews are based. Often times the conclusions of systematic reviews and meta-analyses are considered to provide firm evidence and guidance for practice, even though the underpinning scientific evidence does not. One is tempted to conclude that currently we do not need more systematic reviews here, but we rather need a much stronger original research base of high quality.

It is also worth noting that the term "probiotics" is still very widely used in related publications, even though one has no reason to expect that the multitude of different bacterial strains and interventions included under this term would induce similar biological effects. In fact, the European Commission has banned the use of „probiotic" for food products as an unacceptable health claim, along with the use of terms such as "living" or "active" bacteria, given that any possible effects on health can only be characterised for specific bacterial strains in defined dosages and under defined conditions of use, but not for a product category of "probiotics" as a whole.

## Conclusions

The European Action Plan on Childhood Obesity has identified eight key areas that should receive particular attention with regards to addressing the challenge of childhood obesity. These include i.a. the support of a healthy start into life, the need to monitor and evaluate potential preventive strategies, and the need to increase research in this area. Multiple research opportunities exist for exploring the numerous factors related to the early origins of obesity, which may inform future strategies towards halting the rise in obesity prevalence (Fig. 3). In this context, exploring the effects of the early development of the microbiome is a promising area that should receive further attention. It appears worthwhile to explore not only the impact of supplementing single bacterial strains, but to invest more in exploring the biological complexity of the gut microbiome, the dependence of this ecosystem on dietary and other exogenous factors, and its metabolic and regulatory functions. One would consider that the likelihood of achieving meaningful progress is higher through the combination of several strategies (Fig. 3), rather than by focussing an isolated single strategy.

*Koletzko B. Childhood obesity: current situation and future opportunities. J Pediatr Gastro Nutr 2016 Jul;63 Suppl 1:S18-21. doi: 10.1097/MPG.0000000000001220*

**Financial support and sponsorship**

The work of the author is carried out with partial financial support from the Commission of the European Communities, the 7th Framework Programme Early Nutrition (FP7-289346), the Horizon 2020 research and innovation programme DYNAHEALTH (No 633595), and the European Research Council Advanced Grant META-GROWTH (ERC-2012-AdG – no.322605). This manuscript does not necessarily reflect the views of the Commission and in no way anticipates the future policy in this area. Additional support from the German Ministry of Education and Research, Berlin (Grant Nr. 01 GI 0825) and the University of Munich Innovative Research Priority Project MC-Health is gratefully acknowledged.

**Conflicts of interest**

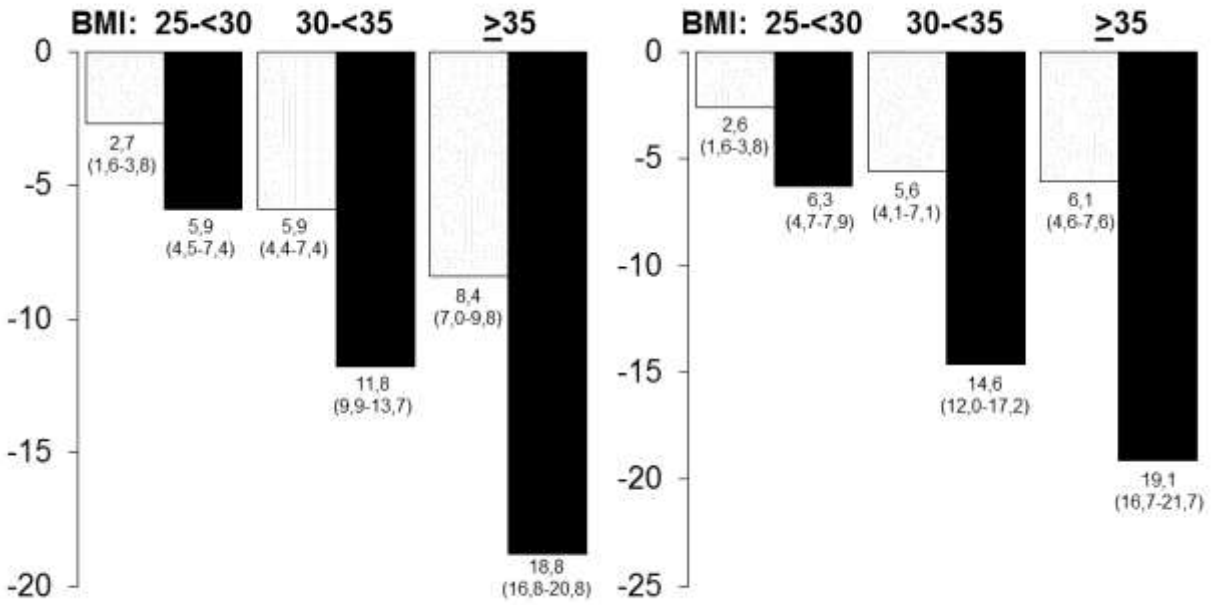
The author is a member of the National Breastfeeding Committee and tends to be biased towards breastfeeding. The Ludwig-Maximilians-Universität München and it's employee BK have received support for scientific and educational activities by a variety of companies, including Abbott Nutrition, Baxter, B. Braun, Coca Cola, Dairy Goat Cooperative, Danone, Fonterra, Fresenius Kabi, Hipp, Mead Johnson, and Nestlé, predominantly as part of publically funded research projects with support of the European Commission or German governmental research support. None of this support has influenced the writing and conclusions of this manuscript.

Table 1: Results of a literature search in the PubMed database of the U.S. National Library of Medicine performed on 8 March 2016 using the search terms using the search terms "probiotic* AND health"or "probiotic* AND obesity" with either "randomized clinical trial"or "systematic review" revealed 3.2 times as many systematic reviews (SR) than randomized clinical trials (RCTs).

| | Probiotics and health | Probiotics and obesity |
|---|---|---|
| Systematic reviews (SR) | 1597 | 244 |
| Randomized clinical trials (RCT) | 498 | 244 |
| Ratio SR/RCT | 3.21 | 7.87 |

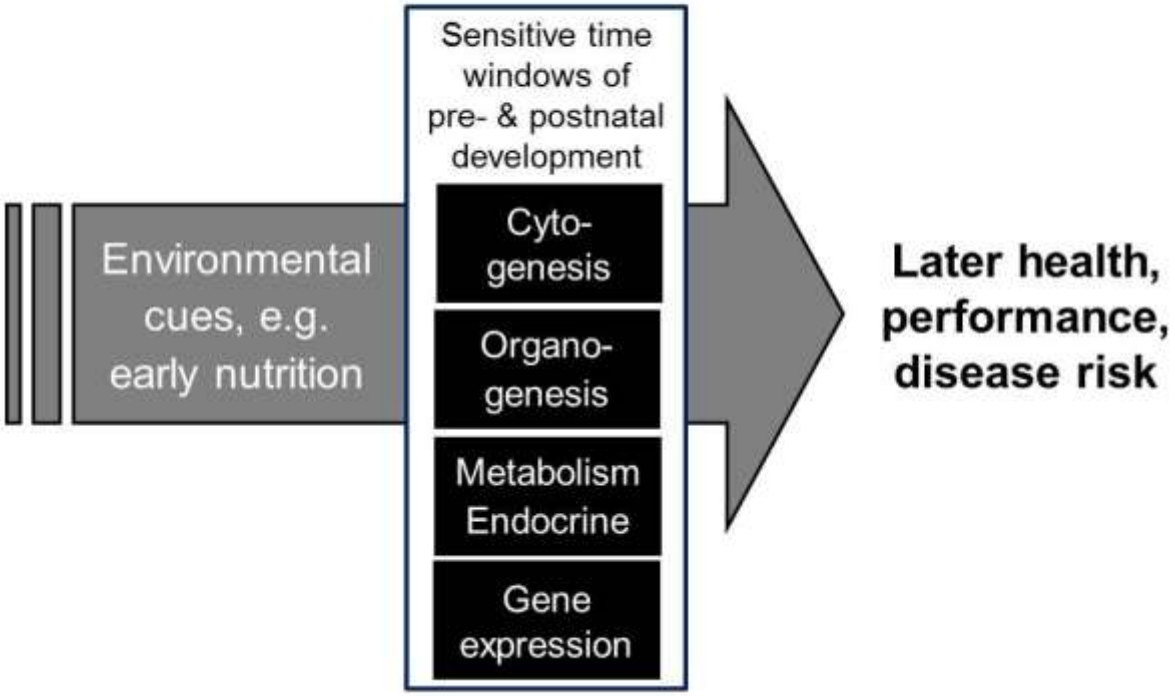
*Koletzko B. Childhood obesity: current situation and future opportunities. J Pediatr Gastro Nutr 2016 Jul;63 Suppl 1:S18-21. doi: 10.1097/MPG.0000000000001220*

Figure 1: Loss of life years (grey bars) and of healthy life years (black bars) in men (left panel) and women (right panel) aged 20 to 39 years by category of the body mass index (BMI). Overweight leads to the loss of ≈6 healthy life years, severe obesity with a BMI <35 to the loss of ≈19 healthy life years. Drawn from data of (2).



*Koletzko B. Childhood obesity: current situation and future opportunities. J Pediatr Gastro Nutr 2016 Jul;63 Suppl 1:S18-21. doi: 10.1097/MPG.0000000000001220*

Figure 2: Environmental cues such as nutrition during sensitive pre- and postnatal periods of developmental plasticity can modulate cyto- and organogenesis, metabolic and endocrine response, and the epigenetic regulation of gene expression, and thereby modulate long-term health, performance and disease risk. Redrawn after (11).



*Koletzko B. Childhood obesity: current situation and future opportunities. J Pediatr Gastro Nutr 2016 Jul;63 Suppl 1:S18-21. doi: 10.1097/MPG.0000000000001220*

Figure 3: Multiple research opportunities exist for exploring the numerous factors related to the early origins of obesity, and which may inform future strategies towards halting the rise in obesity prevalence. It appears likely that progress can be achieved the combination of several strategies, rather than by an isolated single strategy.

**References**

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014 Aug 30;384(9945):766-81.
2. Grover SA, Kaouache M, Rempel P, Joseph L, Dawes M, Lau DC, et al. Years of life lost and healthy life-years lost from diabetes and cardiovascular disease in overweight and obese people: a modelling study. The lancet Diabetes & endocrinology. 2015 Feb;3(2):114-22.
3. Commission-of-the-European-Communities. EU Action Plan on Childhood Obesity 2014-2020. Brussels: Commission of the European Communities; 2014.
4. Koster I, Huppertz E, Hauner H, Schubert I. Costs of Diabetes Mellitus (CoDiM) in Germany, direct per-capita costs of managing hyperglycaemia and diabetes complications in 2010 compared to 2001. Exp Clin Endocrinol Diabetes. 2014 Oct;122(9):510-6.
5. Commission-on-ending-childhood-obesity. Report of the commission on ending childhood obesity. Geneva: World Health Organisation; 2016.
6. Sonntag D, Ali S, deBock F. Estimating the Lifetime Indirect Cost of Childhood Overweight and Obesity: A Markov Modelling Study. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2015 Nov;18(7):A734.
7. Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. Cochrane Database Syst Rev. 2009(1):CD001872.
8. Waters E, de Silva-Sanigorski A, Hall BJ, Brown T, Campbell KJ, Gao Y, et al. Interventions for preventing obesity in children. Cochrane Database Syst Rev. 2011(12):CD001871.
9. Committee-on-obesity-prevention-policies-for-young-children. Early childhood obesity prevention policies. Washington D.C:: Institute of Medicine. The National Academic Press; 2011.
10. Cunningham SA, Kramer MR, Narayan KM. Incidence of childhood obesity in the United States. N Engl J Med. 2014 Apr 24;370(17):1660-1.
11. Koletzko B, Brands B, Chourdakis M, Cramer S, Grote V, Hellmuth C, et al. The Power of Programming and the EarlyNutrition Project: Opportunities for Health Promotion by Nutrition during the First Thousand Days of Life and Beyond. Ann Nutr Metab. 2014;64(3-4):187-96.
12. Brands B, Demmelmair H, Koletzko B. How growth due to infant nutrition influences obesity and later disease risk. Acta Paediatr. 2014 Jun;103(6):578-85.
13. Brands B, Demmelmair H, Koletzko B, The EarlyNutrition P. How growth due to infant nutrition influences obesity and later disease risk. Acta Paediatr. 2014 Feb 12.
14. Koletzko B, Brands B, Poston L, Godfrey K, Demmelmair H, Early Nutrition P. Early nutrition programming of long-term health. Proc Nutr Soc. 2012 Aug;71(3):371-8.
15. Dodd JM, Turnbull D, McPhee AJ, Deussen AR, Grivell RM, Yelland LN, et al. Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial. BMJ. 2014;348:g1285.
16. Yu ZB, Han SP, Zhu GZ, Zhu C, Wang XJ, Cao XG, et al. Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. Obes Rev. 2011 Jul;12(7):525-42.
17. Koletzko B, Chourdakis M, Grote H, Hellmuth C, Prell C, Rzehak P, et al. Regulation of early human growth: impact on long-term health. Ann Nutr Metab. 2014;64:141–50.
18. Koletzko BvK, R.Monasterolo, R. C.Subias, J. E.Scaglioni, S.Giovannini, M.Beyer, J.Demmelmair, H.Anton, B.Gruszfeld, D.Dobrzanska, A.Sengier, A.Langhendries, J. P.Cachera,

M. F.Grote, V. Infant feeding and later obesity risk. Adv Exp Med Biol. [ Bücher und Monographien]. 2009;646:15-29.
19. Arenz SR, R.Koletzko, B.von Kries, R. Breast-feeding and childhood obesity--a systematic review. Int J Obes Relat Metab Disord. [ Bücher und Monographien]. 2004 Oct;28(10):1247-56.
20. Horta BL, Victora CG. Long-term effects of breastfeeding. A systematic review. Geneva: World Health Organisation; 2013.
21. Yan J, Liu L, Zhu Y, Huang G, Wang PP. The association between breastfeeding and childhood obesity: a meta-analysis. BMC Public Health. 2014;14:1267.
22. Weber M, Grote V, Closa-Monasterolo R, Escribano J, Langhendries JP, Dain E, et al. Lower protein content in infant formula reduces BMI and obesity risk at school age: follow-up of a randomized trial. Am J Clin Nutr. 2014 May;99(5):1041-51.
23. Koletzko BK, RudigerClosa, RicardoEscribano, JoaquinScaglioni, SilviaGiovannini, MarcelloBeyer, JeannetteDemmelmair, HansGruszfeld, DariuszDobrzanska, AnnaSengier, AnneLanghendries, Jean-PaulRolland Cachera, Marie-FrancoiseGrote, VeitEuropean Childhood Obesity Trial Study, GroupXhonneux, AnnickVan Hees, Jean-NoelMartin, FrancoiseStolarczyk, AnnaSocha, JerzySocha, PiotrJanas, RomanPietraszek, EwaVerwied-Jorky, SabineSchiess, SoniaPawellek, IngridHandel, UschiHannibal, IrisFritsch, MichaelaGroebe, HelfriedReith, AnnaHofmann, RenateHoyos, JoanaGoyens, PhilippeCarlier, ClotildeDain, ElenaLuque Moreno, VeronicaMendez Riera, GeorginaTedeschi, SabrinaAgostoni, CarloVecchi, FiammettaVerduci, Elvira. Lower protein in infant formula is associated with lower weight up to age 2 y: a randomized clinical trial. The American journal of clinical nutrition. 2009;89(6):1836-45.
24. Koletzko B, Demmelmair H, Grote V, Prell C, Weber M. High protein intake in young children and increased weight gain and obesity risk. Am J Clin Nutr. 2016 Feb;103(2):303-4.
25. Pei Z, Heinrich J, Fuertes E, Flexeder C, Hoffmann B, Lehmann I, et al. Cesarean delivery and risk of childhood obesity. J Pediatr. 2014 May;164(5):1068-73 e2.
26. Mekkes MC, Weenen TC, Brummer RJ, Claassen E. The development of probiotic treatment in obesity: a review. Benefic microbes. 2014;5(1):19-28.