Chapter

Introductory Chapter: Impact of First 1000 Days Nutrition on Child Development and General Health

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1. Introduction

The concept of the first 1000 days refers to the period from conception through the age of 2 years. This period is very crucial for the growth and development of the fetus and child and its long-term health outcomes. Many factors influence this period, including maternal health, breast and complementary feeding, and socioeconomic factors. Biological and metabolic development might be affected permanently by nutritional interventions, leading to adaptive pathophysiological alteration later in childhood and/or adulthood, such as noncommunicable diseases like diabetes mellitus, cardiovascular and chronic respiratory diseases, cancers and neurodegenerative disorders [1], as well as obesity and its adverse consequences [2]. In other words, children's and adults' health risks may be programmed by the nutritional status during this period. The first scientist who raised the theory of the possible effect of inherited genes and environmental factors during this critical period as an origin for the adult disease was Professor David Barker during the 1980s of the last century [3]. Barker affirmed, "Much of human development is completed during the first 1000 days after conception." His theory was later evolved in the Developmental Origin of Health and Disease (DOHaD) theory [4].

This introductory chapter aims to discuss the effects of nutrition, during pregnancy through the age of 2 years, on the health and development of the child and adult and the potential underlying mechanisms.

2. First 1000 days and overweight and/or obesity

Overweight and obesity are defined as an abnormal or excessive accumulation of fat that may impair health. It is a very common problem worldwide, and according to WHO an estimated 38.2 million children under the age of 5 were overweight or obese in 2019 and 340 million children and adolescents aged 5–19 were overweight or obese in 2016 [5]. Obese children are more likely to become obese adults, and in 2016, more than 1.9 billion adults aged 18 years and older were overweight and of these 650 million adults were obese. The problem is increasing and the worldwide prevalence of obesity nearly tripled between 1975 and 2016 [5]. There is increasing evidence that the origins of obesity are within the first 1000 days of life [6]. Prevention of childhood obesity is a public health priority and as it the source for adult obesity, early intervention is recommended. Effective and affordable preventive strategies that are embedded in the existing health system are needed.

These strategies should start early in life, should not be resource intensive, and can be maintained for the long term [7–10].

Risk factors' list for childhood obesity is wide, and antecedents are multifactorial, including genetic/epigenetic, social, biological, environmental, dietary, and behavioral influences. Among these, the most important modifiable risk factors during pregnancy and early childhood are maternal overweight/obesity, gestational weight gain, feeding practice during the first 2 years of life, in addition to maternal general health and smoking during pregnancy, physical activity, and sleep duration [6].

Although the fetal origin of the disease is an old theory dating back to about 40 years ago [3], focusing on its role in the prevention of childhood overweight/obesity is recent. Aspects of nutritional programming are variable, and some aspects may result in a modification in organs or endocrine structures and their function, resulting in irreversible lifelong consequences, and other aspects can be corrected with repeated learned exposure as in early flavor programming for later acceptance of taste/flavor [6]. Childhood obesity is a multifactorial problem. Both acquired and environmental factors can induce effects on genetic expression, and with appropriate interventions, some of the epigenetic changes can be reversed or modified [11]. Several of these modifiable factors have been identified and well studied at the individual level. The most important are maternal feeding behavior during pregnancy and feeding practice behavior during the first 2 years of life. Generally, these factors can be categorized as food and diet behavior (maternal BMI and the rate of increase weight during pregnancy, breastfeeding, age of introduction of complementary feeding, fruit and vegetable intake, sweetened beverage consumption, and the rate of infant weight gain) or feeding and associated lifestyle behavior (maternal smoking, maternal diabetes mellitus and gestational diabetes, sleep duration or screen watching time, use of a pacifier, physical activity, parental inattention to child hunger and satiety, and the parental use of rewarding, controlling, and restrictive feeding practice behavior) [12–14].

A good example of how maternal diet affects the nutritional and metabolic programming of infants as well as his food preference is flavor programming, in which shaping infant food preferences is rooted to fetus exposure via amniotic fluid, and after the development of taste bud, it is from maternal diet preference during pregnancy. As such, the infant shows preference to carrot-flavored cereal in his complementary food when his mother consumed carrot-flavored water during the latter part of pregnancy [15].

Prevention of childhood obesity is also related to infant feeding during the first 2 years of life. Healthy growth of infants requires breastfeeding started as early as possible after birth and the introduction of nutritious complementary food at an appropriate time. Weight gain during the first year of life is one of the best predictors for later obesity [16]. When compared with formula feed counterparts, infants on breastfeeding have a lower percentage of body fat accumulation and in turn lower weight gain and risk for obesity [17]. Three meta-analyses of observational studies found that the obesity risk at school age was reduced by 15–25% with early breastfeeding compared with formula feeding. Additionally, 4% lower obesity prevalence at a later age for each additional month of breastfeeding had been reported [18].

There is no consistent evidence that the introduction of complementary feeding before the age of 4 months is associated with higher later risk for obesity when compared with the introduction of infant complementary feeding between 4 and 6 months or at 6 months age. A study involving a systematic review of the literature investigating the relationship between the introduction of complementary feeding time and overweight or obesity during childhood concludes that the risk of childhood overweight

and obesity has no clear association with the timing of the introduction of complementary foods, although some evidence suggests that very early introduction (at or before 4 months), rather than at 4–6 months or more than 6 months, may increase the risk of childhood overweight [19].

Complementary diet quantity and quality, and in turn energy intake, may also play a role in the acquisition of subsequent childhood obesity. A large study that followed 881 infants in the United Kingdom shows that a higher prevalence of greater weight gain between birth and 1–3 years of age can be predicted in infants who were provided with solid foods at the age of 4 months [20].

Higher dietary protein intake during infancy, in particular from infant formula, had been found to be associated with a higher risk of obesity during the first 6 years of life [18, 21]. One explanation is given through early protein hypothesis, which describes the increasing level of insulin and insulin-like growth factor-1 as a result of high protein intake in early life, resulting in increased fat deposition and weight gain [18]. Apart from sweetened beverage intake, total carbohydrate intake during complementary feeding seems not to be associated with a higher risk of later childhood obesity [22]. Most of the studies about the role of fat intake during infancy in the development of childhood obesity failed to show a positive relationship. Although, one large study from China concludes that fat intake as fish liver oil is associated with a higher risk of childhood overweight [23, 24].

Measures to decrease the risk of obesity through the behavioral changes and nutritional education are found to be most effective during early life. Furthermore, human biology is the most pliable and amenable to changes during this period [25, 26].

3. First 1000 days nutrition and respiratory diseases

Susceptibility to the development of respiratory disease and its progression is affected by nutrition and feeding during the first 1000 days through epigenetic mechanisms [27]. Additionally, nutrition might affect the development of microbiota, which in turn can impress inflammatory, allergic, and immune mechanisms, rendering some individuals more susceptible to the various respiratory diseases of various mechanisms [28]. A study by Mayor et al. in 2015 shows that placental developmental and fetal growth is affected by poor maternal nutrition, resulting in increased susceptibility to noncommunicable diseases. This study in particular revealed that a high maternal fat diet intake before and during pregnancy increased glucose and insulin levels, leading to placental inflammation resulting in placental insufficiency, intrauterine growth restriction, and alteration of fetal lung development [29]. Fetal lung maturation impairment predisposes the neonate to an increased risk of respiratory distress syndrome at birth and chronic lung disease later on [30]. Furthermore, intake of diets rich in vegetables and fruit in the first and second trimesters is associated with a lower risk for allergic respiratory diseases such as allergic rhinitis and asthma in contrast with a diet rich in vegetable oil, margarine, and processed food [31]. This is very important when we compare Western diet (rich in oil, fast food, and processed food) to the Mediterranean diet (rich in fruit and vegetable, olive oil, fish, cereals, and other fiber diets) as a maternal dietary risk factor for the development of respiratory diseases. The adherence to the Mediterranean diet has been found to be associated with the normalization trend of gut microbiota, making it a good preventive choice for allergic diseases [32]. Some studies show that maternal supplementation with fish source Omega-3 polyunsaturated long-chain fatty acids during pregnancy is associated with a lower risk of allergic sensitization like allergic rhinitis, asthma, and atopic

dermatitis [31, 33, 34]. Additionally, maternal supplementation during pregnancy with micronutrients as Vitamin D and E and zinc is associated with a lower risk for childhood wheezes [35].

The short- and long-term benefits of breastfeeding are beyond doubt. Breastfeeding reduces childhood morbidity and mortality from infectious diseases, including respiratory, because it contains secretory IgA antibodies, anti-inflammatory cytokines, galacto-oligosaccharides, and lactoferrin [36]. The American Academy of Pediatrics reported, in 2012, a 72% reduction of risk of first-year hospitalization in exclusively breastfed infants for the first 4 months of life. Additionally, the severity of RSV bronchiolitis was reduced by 74% when compared with infants who are never or only partially breastfed [37]. WHO, on the other hand, reports that human milk can reduce the rate of hospital admission, severity, and mortality of lower respiratory tract infection by around 50, 30, and 60%, respectively [38].

The increasing incidence of various types of allergic diseases, including allergic rhinitis and asthma, in the last decades, is well documented all over the world, especially in developed countries. Many theories for this raise of incidence have been suggested, such as the urbanization of the population and following of the western lifestyle. Hygiene hypothesis (decreased rate of infectious burden is associated with the increased incidence of allergic disease), tobacco smoking, pollution, sedentary lifestyle, and reduced rate or absence of breastfeeding in the first months of life are thought to be important contributors [31]. In the first year of life, exposure to a wide range of food antigens is associated with a lower incidence of asthma, allergic rhinitis, and atopic dermatitis. So, the inclusion of food allergen in the first year of life might be protective against allergic diseases especially asthma [31]. Furthermore, maternal diet during pregnancy might have an impact on health even before delivery, and some interventional studies report immunomodulatory effects of specific nutrients on the neonate and a reduction of early sensitization to allergens [39, 40]. The proposed mechanisms are mainly immunological, suggesting the key role of diet in the hemostasis of the immune system, leading to oral tolerance and preventing excessive reactions to innocuous antigens which lead to allergic disease.

The role of breastfeeding in preventing allergic respiratory disease is controversial. Some studies have addressed the protective effect of breast feeding on the development of allergic diseases during childhood by facilitating the development of host immune mechanisms especially against allergic rhinitis in the first 5 years of life, while the evidence for the association between breastfeeding and wheezing and asthma was inconclusive [41, 42]. On the other hand, a protective effect of exclusive breastfeeding during the first 3 months of life against the development of asthma in children from atopic families has been demonstrated by other recent studies [29].

Many studies have investigated the role of complementary foods' introduction during infancy as a risk factor for developing allergy. Delayed introduction of solid foods has no effects on the prevalence of allergy, a result found by many studies [43, 44]. Recently, many studies investigated the protective effect of early introduction of highly allergenic foods (cow's milk, egg, fish, and peanuts) after at least 3–4 months of exclusive breastfeeding against food allergy [30]. In general, the results of these studies and many others [31, 45, 46] are inconclusive, and further studies, especially in children with a positive family history of atopy, are required to investigate the role of timing of introduction of high allergenic food in the development of atopy.

The effect of type of the diet on the susceptibility to asthma and atopy in children also has been studied. It has been found that Mediterranean type of diet (rich in fruit, vegetable, fibers, seafood, and olive oil) has a protective effect against

asthma and atopy when compared to the western style of diet (rich in saturated fats, red meats and poor in fruit, vegetable, whole grain, and seafood) [33, 47].

The micronutrient also has an important protective effect against respiratory diseases. Those with a potent antioxidant activity may delay the onset, severity, and outcome of asthma. Recent studies conclude that asthma is associated with the boosted production of reactive oxygen and reactive nitrogen species (ROS and RNS) and the pathogenesis of this disease is enhanced by changes in enzymatic antioxidant activity in lung and blood. Furthermore, both ROS and RNS increase systemic oxidative stress and subsequently increase the oxidative burden due to the alteration of systemic and blood antioxidant systems, which is typical of bronchial asthma. Wherefore, improvement of antioxidant activity may represent a successful strategy for delaying the onset, decreasing the severity, and improving the outcome of asthma. The most important antioxidants in this regard are vitamin E, vitamin C, selenium, coenzyme Q10, and carotene [48]. Zinc and iron have an important role in the immune system. Zinc is thought to inhibit the viral replication or intracellular adhesion and boost immune response at mucosal surfaces and hence may have a protective effect against the upper respiratory tract infections. Iron, on the other hand, has an important role in cytokines secretion, T cell proliferation, and bactericidal activity. Iron deficiency might impair these functions [48].

Vitamins also play a role in the defense mechanisms against respiratory diseases. Vitamin A is important for the enhancement of immune function and may limit the severity of respiratory infections in children older than 5 years of age [30]. Vitamin D, on the other hand, probably affects the onset, severity, and exacerbation of asthma, respiratory tract infections, and chronic obstructive airway diseases. Many theories have been adopted to explain this effect of vitamin D, including modulating immune mechanisms [49] and its influences on fetal lung maturation and airway smooth muscle cell proliferation and differentiation per via paracrine [50]. The role of vitamin C in the prevention and treatment of common cold is well known. By its potent antioxidant proprieties, vitamin C counteracts oxidants and decreases the external attacks of bacteria, viruses, toxins, and xenobiotics in the lung and hence modulates the development of bronchial inflammation and the impairment of pulmonary function [30, 51]. Contrary to the positive effects of the above vitamins, some studies show that folic acid (commonly used as a preventive measure for neural tube defects) in high dose given after the first trimester has been associated with an increased incidence of childhood asthma and eczema [30]. This relationship has not been documented by many other studies [52, 53].

4. First 1000 days nutrition and brain development

Throughout life, the first 1000 days represent the most vulnerable period for brain development and growth. During this period, the brain grows more rapidly than any other time, and it is the period where the neuronal connection and proper cognitive functioning occurs. Nutritional needs should be met during this period to ensure proper growth and development of the brain. A lifelong deficit may result from failure to provide key nutrients during this critical period despite subsequent nutrient repletion [54].

Development of the brain started 16 days after conception, growing throughout pregnancy, and taking adult form by 7 months of gestation [55]. Protein, fat and fatty acids, zinc, iron, folate, and iodine are required for neuronal creation, myelination, and synapses formation. Inadequate intake for these nutrients and micronutrients might impair the neurodevelopmental process [56].

Nutrition during the first 2 years of life is essential for this critical period of brain development and growth. Motor functions such as posture, balance, and coordination and the child's ability to create and recall memories (hippocampal—prefrontal connection) are well known to develop during this period [57]. Breastfeeding is the idealistic food for brain growth and development during the first 2 years of life as it contains hormones, growth factors, and a variety of nutrients that are essential for this process. Deoni et al., in their cross-sectional study in 2013, conclude that infant breastfeeding is associated with improved developmental growth in late-maturing white matter association regions, and extended breastfeeding duration is associated with improved white matter structure and cognitive performance [58]. Furthermore, extreme preterm infants fed predominatingly with breast milk in the first 28 days of life show a greater deep nuclear gray matter volume, and by the age of 7 years, they had higher IQs and better scores in reading, mathematics, working memory, and motor function tests [59]. Breastfeeding provides not only the first-class nutrition necessary for the shaping of the brain but also affects the quality of the experiences and interactions they have with caregivers, which is found to be critical for both the cognitive and socio-emotional development [60].

5. First 1000 days nutrition and probiotics

The term dysbiosis refers to the microbial imbalance inside the human, especially digestive tract. In the last two decades, there was a great interest in the human microbiome. Thousands of studies were conducted to highlight its impact on health and disease. More than 500 bacteria species were found harboring the digestive tract, representing about 25 times more genes than the human genome [61, 62]. These microbes are thought to play a vital role in human health through protection against pathogenic microorganisms, metabolic functions by fermentation of indigestible carbohydrates, and modulation of the human immune system. Furthermore, recently there is important evidence to link dysbiosis with many human diseases like allergy, asthma, obesity, and inflammatory bowel diseases [63–65]. The gut of newborns will be rapidly colonized by microbes immediately after birth from exposure to the mother's microbiota, especially from the vagina and fecal material. Later on, feeding, close physical contact like hugging and kissing, and the environment will be the source of microbes. The adult pattern of gut microbiota will be established by the age of 3 years [66]. The establishment of the gut bacterial patterns is greatly influenced by the type of feeding. Breast milk is rich in complex nondigestible oligosaccharides, with more than 200 different molecules [67]. These oligosaccharides are resistant to hydrolysis by human small intestine enzymes and reach the large intestine, acting as substrates for microorganisms there, promoting the growth of specific bacteria. Nowadays, most infant formulas are supplemented with oligosaccharides, in particular fructo- and galacto-oligosaccharides, with the aim to improve the intestinal microbiota in early life [68]. Early dysbiosis that resulted from different factors like cesarean sections, prematurity, and early exposure to antibiotics might be associated with a wide spectrum of diseases like obesity, allergic disease, and autism spectrum disorders as revealed by several epidemiological studies [68, 69].

6. First 1000 days and epigenetics

Epigenetic modifications of the expression of genes occur through several mechanisms including DNA methylation, histone modifications, and posttranscriptional

gene-silencing by noncoding microRNAs [1]. Modifications to the epigenetic profile by external and internal environments of the cell can have short-term and long-term effects on gene expression [70–72]. A range of environmental stressors have epigenetic effects that are associated with diseases [70]. Some of these stressors include tobacco smoke-related diseases, air pollution effects on immunity and inflammatory responses, endocrine disrupting compounds, and others [73, 74].

Studies of the impact of environmental stressors on the epigenome provide insights into the mechanisms that link those stressors with the subsequent manifestations of disease. Such studies are especially important in establishing a full understanding of the linkage between stressor-induced modifications of the epigenome during the initial 1000 days and maternal and neonatal nutrition. At this time, most human studies have been aimed at characterizing the degree of association between epigenetic modifications and environmental stressors. Many of these studies use methodologies that characterize changes in global DNA methylation patterns or methylation of a limited subset of specific genes of interest in cord blood or maternal or neonatal peripheral blood samples. The methylation patterns are then used as biomarkers to correlate with the developmental abnormalities and disease status. A few examples are summarized here.

Maternal folate nutrition during pregnancy has been implicated in several birth defects [75]. The mechanisms that underlie DNA methylation are dependent on dietary folate and one-carbon metabolism [76]. Methylation profiles of a number of genes, including some not normally associated with folate biology, have a significant association with the maternal plasma folate during pregnancy [77]. Maternal serum folate concentrations are associated with DNA methylation patterns of seven genomic regions observed in the neonatal cord blood, especially in a region upstream of a regulator of DNA methylation during development [78]. Methylation patterns of insulin-like growth factor-2 (*IGF2*) in children are associated with the maternal periconceptional supplementation of folic acid [79]. Others have observed that the methylation patterns of *IGF2* promoter regions are not associated with the folate concentrations in maternal blood or cord blood [80]. On the other hand, the latter study did report an association between the serum levels of vitamin B12 in maternal blood and methylation patterns in one of the *IGF2* promoters. Vitamin D supplementation of pregnant and lactating women also has been associated with differential epigenome-wide DNA methylation patterns in their breastfed infants [81]. Specific effects of folate and other nutrients on epigenetic alterations in the fetus or newborn continue to be the areas of active investigation.

Toxic metal (arsenic, mercury, cadmium, and lead) exposure during pregnancy is associated with epigenomic changes in the offspring [82, 83]. Similarly, epigenomic changes in the offspring have been found associated with the exposure to endocrine disruptors, such as bisphenol-a, dichlorodiphenyltrichloroethane, polybrominated diphenyl ethers, polychlorinated biphenyls, and phthalates [83]. The relationship between these types of observed associations of epigenetic changes and environmental stressors during pregnancy and early life and their relationship with the known effects of those stressors and childhood and adult health remain to be understood.

Prenatal exposure to famine is associated with less methylation of the insulin-like growth factor-2 (*IGF2*) gene observed in adults six decades later [84]. That study underscores the potential for early life environmental stressors to cause long-term epigenetic modifications. Prenatal exposure to other environmental stressors on the mother, such as smoking, asthma, immune stress during pregnancy, and obesity, are associated with differences in the DNA methylation patterns of peripheral blood cells when comparing children who develop asthma with those who do not develop the condition [85].

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References

[1] Agosti M, Tandoi F, Morlacchi L. Angela Bossi. Nutritional and metabolic programming during the first thousand days of life. La Pediatria Medica e Chirurgica. 2017;**39**:157. DOI: 10.4081/pmc.2017.15

[2] Blake-Lamb TL, Locks LM, Perkins ME, Woo Baidal JA, Cheng ER, Taveras EM. Interventions for childhood obesity in the first 1,000 days: A systematic review. American Journal of Preventive Medicine. 2016;**50**(6):780-789. DOI: 10.1016/j.amepre.2015.11.010. Epub 6 Feb 22

[3] Barker DJ. The fetal and infant origins of adult disease. BMJ. 1990;**301**:1111

[4] Wadhwa PD, Buss C, Entringer S, Swanson JM. Developmental origins of health and disease: Brief history of the approach and current focus on epigenetic mechanisms. Seminars in Reproductive Medicine. WHO Fact Sheet. 2009;**27**(5):358-368. DOI: 10.1055/s-0029-1237424. Available from: https://www.who.int/news-room/fact sheets/detail/obesity-and-overweight

[5] WHO Fact Sheet. Available from: https://www.who.int/news-room/fact sheets/detail/obesity-and-overweight

[6] Black RE, Makrides M, Ong KK, editors. Complementary feeding: Building the foundations for a healthy life. In: Nestlé Nutr Inst Workshop Ser. Vol. 87. Basel: Nestec Ltd., Vevey/S. Karger AG; 2017. pp. 183-196. DOI: 10.1159/000448966

[7] Wake M. The failure of anti-obesity programmes in schools. BMJ. 2018;**360**:k507

[8] Blake-Lamb TL, Locks LM, Perkins ME, et al. Interventions for childhood obesity in the first 1,000 days a systematic review. American Journal of Preventive Medicine. 2016;**50**(6):780-789

[9] World Health Organization. Consideration of the evidence on childhood obesity for the commission on ending childhood obesity. In: Report of the ad hoc Working Group on Science and Evidence for Ending Childhood Obesity. Geneva, Switzerland: World Health Organization; 2016

[10] Waters E, de Silva-Sanigorski A, Hall BJ, et al. Interventions for preventing obesity in children. Cochrane Database of Systematic Reviews. 2011;**12**:CD001871

[11] World Health Organization. Interim Report of the Commission on Ending Childhood Obesity. Geneva: WHO; 2015

[12] Dattilo AM, Birch L, Krebs NF, et al. Need for early interventions in the prevention of pediatric overweight: A review and upcoming directions. Journal of Obesity. 2012;**2012**:123023

[13] Weng SF, Redsell SA, Swift JA, et al. Systematic review and meta-analyses of risk factors for childhood overweight identifiable during infancy. Archives of Disease in Childhood. 2012;**97**:1019-1026

[14] Woo Baidal JA, Locks LM, Cheng ER, Blake-Lamb TL, Perkins ME, Taveras EM. Risk factors for childhood obesity in the first 1000 days: A Systematic Review. American Journal of Preventive Medicine. 2016;**50**(6):761-779. DOI: S0749-3797(15)00752-7

[15] Shin D, Lee KW, Song WO. Pre-pregnancy weight status is associated with diet quality and nutritional biomarkers during pregnancy. Nutrients. 2016;**8**:162

[16] Ong KK, Loos RJ. Rapid infancy weight gain and subsequent obesity:

Systematic reviews and hopeful suggestions. Acta Paediatrica. 2006;**95**:904-908

[17] Dewey KG. Growth characteristics of breastfed compared to formula-fed infants. Biology of the Neonate. 1998;**74**:94-105

[18] Koletzko B, von Kries R, Closa R, et al. Can infant feeding choices modulate later obesity risk? The American Journal of Clinical Nutrition. 2009;**89**:1502S-1508S

[19] Pearce J, Taylor MA, Langley-Evans SC. Timing of the introduction of complementary feeding and risk of childhood obesity: A systematic review. International Journal of Obesity. 2013;**37**(10):1295-1306. DOI: 10.1038/ijo.2013.99

[20] Ong KK, Emmett PM, Noble S, et al. Dietary energy intake at the age of 4 months predicts postnatal weight gain and childhood body mass index. Pediatrics. 2006;**117**:e503-e508

[21] Weber M, Grote V, Closa-Monasterolo R, et al. Lower protein content in infant formula reduces BMI and obesity risk at school age: Follow-up of a randomized trial. The American Journal of Clinical Nutrition. 2014;**99**:1041-1051

[22] Pan L, Li R, Park S, et al. A longitudinal analysis of sugar-sweetened beverage intake in infancy and obesity at 6 years. Pediatrics. 2014;**134**(suppl 1):S29-S35

[23] Butte NF, Fox MK, Briefel RR, et al. Nutrient intakes of US infants, toddlers, and preschoolers meet or exceed dietary reference intakes. Journal of the American Dietetic Association. 2010;**110**:S27-S37

[24] Zheng JS, Liu H, Zhao YM, et al. Complementary feeding and childhood adiposity in preschool-aged children in a large Chinese cohort. The Journal of Pediatrics. 2015;**166**:326-331

[25] Contento IR. Nutrition education: Linking research, theory, and practice. Asia Pacific Journal of Clinical Nutrition. 2008;**17**(Suppl 1):176-179

[26] World Health Organization. Health Education: Theoretical Concepts, Effective Strategies and Core Competencies: A Foundation Document to Guide Capacity Development of Health Educators. Geneva: WHO; 2012

[27] Barker DJP. Developmental origins of chronic disease. Public Health. 2012;**126**:185-189

[28] Di Mauro A, Neu J, Riezzo G, Raimondi F, Martinelli D, Francavilla R, et al. Gastrointestinal function development and microbiota. Italian Journal of Pediatrics. 2013;**39**:15

[29] Mayor RS, Finch KE, Zehr J, Morselli E, Neinast MD, Frank AP, et al. Maternal high-fat diet is associated with impaired fetal lung development. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2015;**309**:360-368

[30] Verducia E, Martellib A, Minielloc VL, et al. Nutrition in the first 1000 days and respiratory health: A descriptive review of the last five years' literature. Allergol Immunopathol (Madr). 2017;**45**(4):405-413

[31] Julia V, Macia L, Dombrowicz D. The impact of diet on asthma and allergic diseases. Nature Reviews. Immunology. 2015;**15**:308-322

[32] Bifulco M. Mediterranean diet: The missing link between gut microbiota and inflammatory disease. European Journal of Clinical Nutrition. 2015;**69**:1078

[33] Berthon BS, Wood LG. Nutrition and respiratory health --- feature review. Nutrients. 2015;**7**:1618-1643

[34] de Silva D, Geromi M, Halken S, Host A, Panesar SS, Muraro A, et al. Primary prevention of food allergy in children and adults: Systematic review. Allergy. 2014;**69**:581-589

[35] Beckhaus AA, Garcia-Marcos L, Forno E, Pacheco-Gonzalez RM, Celedon JC, Castro-Rodriguez JA. Maternal nutrition during pregnancy and risk of asthma, wheeze, and atopic diseases during childhood: A systematic review and meta-analysis. Allergy. 2015;**70**:1588-1604

[36] Verduci E, Banderali G, Barberi S, Radaelli G, Lops A, Betti F, et al. Epigenetics effects of human breast milk. Nutrients. 2014;**6**:1711-1724

[37] American Academy of Pediatrics (AAP). Section on breastfeeding. Breastfeeding and the use of human milk. Pediatrics. 2012;**129**:e827-e841

[38] Horta BL, Victora CG. Respiratory infection. In: Short Term Effects of Breastfeeding. A Systematic Review on the Benefits of Breastfeeding on Diarrhoea and Pneumonia Mortality. World Health Organization; 2013. pp. 30-33. Available from: http://apps.who.int/iris/bitstream/10665/95585/1/9789241506120 eng.pdf?ua=1 [Accessed: 03 July 2020]

[39] Dunstan JA et al. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: A randomized, controlled trial. The Journal of Allergy and Clinical Immunology. 2003;**112**:1178-1184

[40] Bunyavanich S et al. Peanut, milk, and wheat intake during pregnancy is associated with reduced allergy and asthma in children. The Journal of Allergy and Clinical Immunology. 2014;**133**:1373-1382

[41] Lodge CJ, Tan DJ, Lau MX, Dai X, Tham R, Lowe AJ, et al. Breastfeeding and asthma and allergies: A systematic review and meta-analysis. Acta Paediatrica. 2015;**104**:38-53.15

[42] Cesar GV, Bahl R, Barros AJD, GVA F, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: Epidemiology, mechanisms, and lifelong effect. Lancet. 2016;**387**(10017):475-490

[43] Snijders BE, Thijs C, van Ree R, van den Brandt PA. Age at first introduction of cow milk products and other food products in relation to infant atopic manifestations in the first 2 years of life: The KOALA birth cohort study. Pediatrics. 2008;**122**:e115-e122

[44] Zutavern A, Brockow I, Schaaf B, von Berg A, Diez U, Borte M, et al. Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: Results from the prospective birth cohort study LISA. Pediatrics. 2008;**121**:e44-e52

[45] Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G, et al. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. Allergy. 2014;**69**:590-601

[46] Alessandri C, Zennaro D, Scala E, Ferrara R, Bernardi ML, Santoro M, et al. Ovomucoid (Gal d 1) specific IgE detected by microarray system predict tolerability to boiled hen's egg and an increased risk to progress to multiple environmental allergen sensitisation. Clinical and Experimental Allergy. 2012;**42**:441-450

[47] Castro-Rodriguez JA, Ramirez-Hernandez M, Padilla O, Pacheco-Gonzalez RM, Pérez-Fernández V, Garcia-Marcos L. Effect of foods and Mediterranean diet during pregnancy and first years of life on wheezing, rhinitis and dermatitis in preschoolers. Allergol Immunopathol (Madr).

2016;**44**(5):400-409. DOI: 10.1016/j.aller.2015.12.002

[48] Fabian E, Pölöskey P, Kósa L, Elmadfa I, Réthy LA. Nutritional supplements and plasma antioxidants in childhood asthma. Wiener Klinische Wochenschrift. 2013;**125**:309-315

[49] Hossein-nezhad A, Vitamin Holick MF. D for health: A global perspective. Mayo Clinic Proceedings. 2013;**88**:720-755

[50] Bantz SK, Zhu Z, Zheng T. The role of vitamin D in pediatric asthma. Annals of Pediatrics & Child Health. 2015;**3**:1032

[51] McEvoy CT, Schilling D, Clay N, Jackson K, Go MD, Spitale P, et al. Vitamin C supplementation for pregnant smoking women and pulmonary function in their newborn infants: A randomized clinical trial. Journal of the American Medical Association. 2014;**311**:2074-2082

[52] Granell R, Heron J, Lewis S, Davey Smith G, Sterne JA, Henderson J. The association between mother and child MTHFR C677T polymorphisms, dietary folate intake and childhood atopy in a population-based, longitudinal birth cohort. Clinical and Experimental Allergy. 2008;**38**:320-328

[53] Miyake Y, Sasaki S, Tanaka K, Maternal HY. B vitamin intake during pregnancy and wheeze and eczema in Japanese infants aged 16---24 months: The Osaka Maternal and child health study. Pediatric Allergy and Immunology. 2011;**22**:69-74

[54] Schwarzenberg SJ, Georgieff MK, AAP Committee on Nutrition. Advocacy for improving nutrition in the first 1000 days to support childhood development and adult health. Pediatrics. 2018;**141**(2):e20173716

[55] Couperus JW, Nelson CA. Early brain development and plasticity. In: McCartney K, Phillips D, editors. Blackwell Handbook of Early Childhood Development. Oxford, UK: Blackwell Publishing Ltd.; 2006

[56] Georgieff MK, Rao R, Fuglestad AJ. The role of nutrition in cognitive development. In: Nelson CA, Luciana M, editors. Handbook of Developmental Cognitive Neuroscience. Cambridge, MA: MIT Press; 1999. pp. 491-504

[57] Williams J, Mai CT, Isenbrug J, et al. Updated estimates of neural tube defects prevented by mandatory folic acid fortification in the United States 1995-2011. Morbidity and Mortality Weekly Report. 2015;**64**(01):1-5

[58] Deoni SC, Dean DC 3rd, Piryatinsky I, et al. Breastfeeding and early white matter development: A cross-sectional study. NeuroImage. 2013;**82**:77-86. DOI: 10.1016/j.neuroimage.2013.05.090

[59] Belfort MB, Anderson PJ, Nowak VA, et al. Breast Milk feeding, brain development, and neurocognitive outcomes: A 7-year longitudinal study in infants born at less than 30 Weeks' gestation. The Journal of Pediatrics. 2016;**177**:133-139.e1. DOI: 10.1016/j.jpeds.2016.06.045

[60] Lee H, Park H, Ha E, et al. Effect of breastfeeding duration on cognitive development in infants: 3-year follow-up study. Journal of Korean Medical Science. 2016;**31**(4):579-584. DOI: 10.3346/jkms.2016.31.4.579

[61] Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010;**464**:59-65

[62] Dietert RR, Dietert JM. The microbiome and sustainable healthcare. Healthcare. 2015;**3**:100-129

[63] Butel M, Waligora-Dupriet A, Wydau-Dematteis S. The developing

gut microbiota and its consequences for health. Journal of Developmental Origins of Health and Disease. 2018;**9**(6):590-597. DOI: 10.1017/S2040174418000119

[64] Fujimura KE, Slusher NA, Cabana MD, Lynch SV. Role of the gut microbiota in defining human health. Expert Review of Anti-Infective Therapy. 2010;**8**:435-454

[65] Neish AS. Microbes in gastrointestinal health and disease. Gastroenterology. 2009;**136**:65-80

[66] Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. Nature. 2012;**486**:222-227

[67] Jost T, Lacroix C, Braegger C, Chassard C. Impact of human milk bacteria and oligosaccharides on neonatal gut microbiota establishment and gut health. Nutrition Reviews. 2015;**73**:426-437

[68] Butel M-J, Waligora Dupriet A-J, Wydau-Dematteis S. The developing gut microbiota and its consequences for health. Journal of Developmental Origins of Health and Disease. 2018;**1**:8. DOI: 10.1017/S2040174418000119

[69] Kuzniewicz MW, Wi S, Qian Y, et al. Prevalence and neonatal factors associated with autism spectrum disorders in preterm infants. The Journal of Pediatrics. 2014;**164**:20-25

[70] Kanherkar RR, Bhatia-Dey N, Csoka AB. Epigentics across the human lifespan. Frontiers in Cell and Development Biology. 2014;**2**:1-19

[71] Hochberg Z, Feil R, Constancia M, et al. Child health, developmental plasticity, and epigenetic programming. Endocrine Reviews. 2011;**32**:159-224

[72] Ghantous A, Hernandez-Vargas H, Bymes G, et al. Characterizing the epigenome as a key component of the fetal exposome in evaluating *in utero* exposures and childhood cancer risk. Mutagenesis. 2015;**30**:733-742

[73] Ladd-Acosta C, Shu C, Lee BK, et al. Presence of an epigenetic signature of prenatal cigarette smoke exposure in childhood. Environmental Research. 2017;**144**(Pt A):139-148

[74] Barouki R, Melen E, Herceg Z, et al. Epigenetics as a mechanism linking developmental exposures to long-term toxicity. Environment International. 2018;**114**:77-86.s

[75] Barua S, Kuizon S, Junaid MA. Folic acid supplementation in pregnancy and implications in health and disease. Journal of Biomedical Science. 2014;**21**:77-85

[76] Crider KS, Yang TP, Berry RJ, et al. Folate and DNA methylation: A review of molecular mechanisms and the evidence for folate's role. Advances in Nutrition. 2012;**3**:21-38

[77] Joubert BR, den Dekker HT, Felix JF, et al. Maternal plasma folate impact differential DNA methylation in an epigenome-wide meta-analysis of newborns. Nature Communications. 2016;**7**:10577

[78] Amarasekera M, Martino D, Ashley S, et al. Genome-wide DNA methylation profiling identifies a folate-sensitive region of differential methylation upstream of *ZFP57*-impreinting regulator in humans. The FASEB Journal. 2014;**28**:4068-4076

[79] Steegers-Theunissen RP, Obermann-Borst SA, Kremer D, et al. Periconceptional maternal folic acid use of 400 μg per day is related to increased methylation of the *IGF2* gene in the very young child. PLoS One. 2009;**4**:e7845

[80] Ba Y, Yu H, Liu F, et al. Relationship of folate, vitamin B12 and methylation

of insulin-like growth factor-II in maternal and cord blood. European Journal of Clinical Nutrition. 2011;**65**:480-485

[81] Anderson CM, Gillespe SL, Thiele DK, et al. Effects of maternal vitamin D supplementation on maternal and infant epigenome. Breastfeeding Medicine. 2018;**13**:371-380

[82] Eid A, Zawai N. Consequences of lead exposure, and its emerging role as an epigenetic modifier in the aging brain. Neurotoxicology. 2016;**56**:254-261

[83] Bommarito P, Martin E, Fry RC. Effects of prenatal exposure to endocrine disruptors and toxic metals on the fetal epigenome. Epigenomics. 2017;**9**:333-350

[84] Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. PNAS. 2008;**105**:17046-17049

[85] DeVries A, Donata V. The neonatal methylome as a gatekeeper in the trajectory to childhood asthma. Epigenetics. 2017;**9**:585-593