*Lead Article*

# Early-life nutritional exposures and lifelong health: immediate and long-lasting impacts of probiotics, vitamin D, and breastfeeding

Cristiana Berti, Carlo Agostoni, Riccardo Davanzo, Elina Hyppönen, Erika Isolauri, Helle M. Meltzer, Régine P.M. Steegers-Theunissen, and Irene Cetin

*Pregnancy and infancy comprise the most critical stages for conditioning an individual's health, with a number of implications for subsequent risks of morbidity, mortality, and reproductive health. Nutrition may influence both the overall pregnancy outcome and the growth trajectory and immune system of the fetus and infant, with short- and long-term effects on the health of the offspring. Within this context, leading experts at Expo Milano 2015 in Milan, Italy, discussed up-to-date knowledge while providing suggestions and challenges before, during, and after pregnancy. This narrative review summarizes the key issues raised by the experts concerning the interplay between the nutritional environment from conception to early infancy and the offspring's immediate and lifelong health, with a particular focus on epigenetic mechanisms, probiotics, vitamin D, and breastfeeding. Taken together, the findings strengthen the awareness that nutritional exposures occurring from preconception to the postnatal period may be strong determinants of the offspring's health and may provide supportive evidence for current nutritional recommendations and guidelines for pregnant women and infants. Critical topics to be addressed in future research and translated into recommendations of public health relevance are also highlighted.*

## INTRODUCTION

Pregnancy and infancy comprise the most critical stages for conditioning a human being's health. The interconnected stages, events, and factors that, from preconception to early infancy, influence the offspring's health in both the short and the long term are schematized in Figure 1.

Pregnancy is a dynamic state and consists of a continuum of phases from conception to birth, with the periconceptional period playing a critical role in shaping fetal development.[1,2] Fetal growth depends on

Affiliation: *C. Berti* is with the Department of Biomedical and Clinical Sciences, School of Medicine and Center for Fetal Research Giorgio Pardi, University of Milan, Milan, Italy. *C. Agostoni* is with the Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; and the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy. *R. Davanzo* is with the Division of Neonatology and NICU, Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy. *E. Hyppönen* is with the Centre for Population Health Research, Sansom Institute of Health Research and School of Health Sciences, University of South Australia, Adelaide, Australia; the South Australian Health and Medical Research Institute, Adelaide, Australia; and the Population, Policy and Practice Programme, University College London Institute of Child Health, London, United Kingdom. *E. Isolauri* is with the Department of Paediatrics, Turku University Hospital and University of Turku, Turku, Finland. *H.M. Meltzer* is with the Norwegian Institute of Public Health, Domain of Infection Control and Environmental Health, Oslo, Norway. *R.P.M. Steegers-Theunissen* is with the Department of Obstetrics and Department of Gynaecology, Erasmus MC, University Medical Centre, Rotterdam, the Netherlands. *I. Cetin* is with the Department of Biomedical and Clinical Sciences, School of Medicine and Center for Fetal Research Giorgio Pardi, University of Milan, Milan, Italy

Correspondence: *C. Berti*, Department of Biomedical and Clinical Sciences, University of Milan, via GB Grassi 64, 20157 Milan, Italy. Email: cristiana.berti2@gmail.com. Phone: +39-02503-19618.

*Key words: epigenetics, gut microbiota, infancy, nutrition, pregnancy.*



doi: 10.1093/nutrit/nuw056

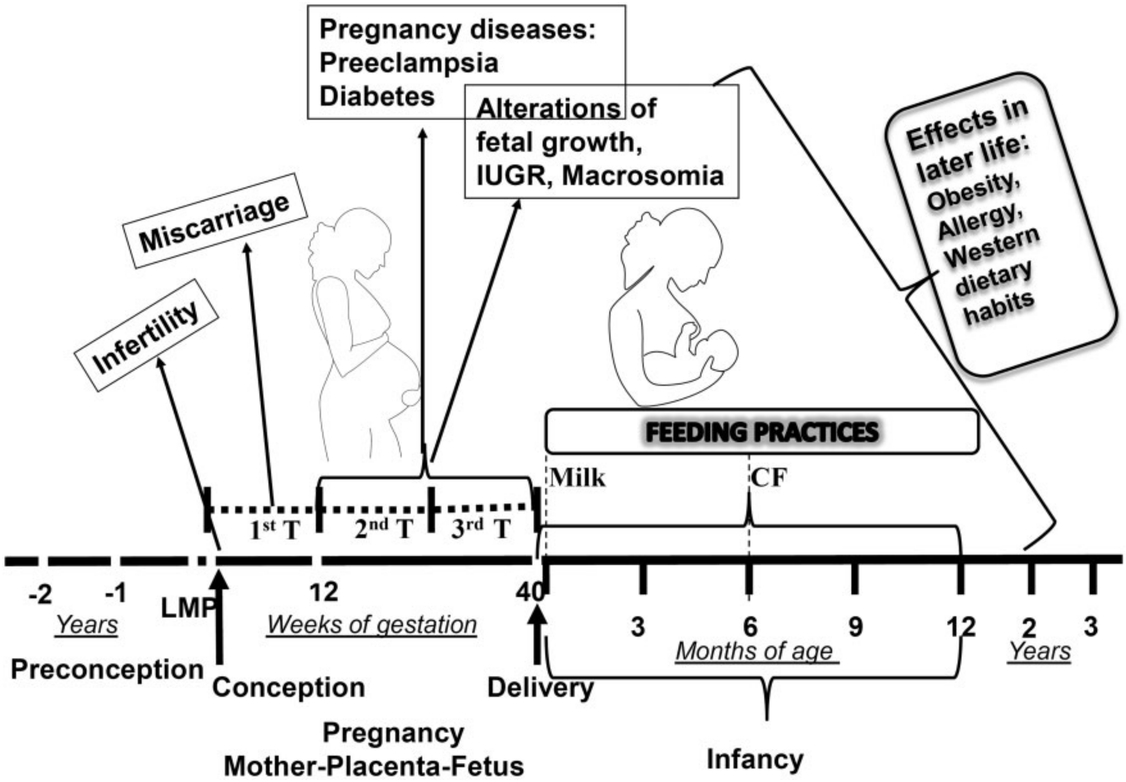


*Figure 1* **The continuum of interplay between a woman of reproductive age, the nutritional environment, and the offspring's lifelong health from conception, through pregnancy, until the cessation of breastfeeding.** Pregnancy consists of uninterrupted stages from preconception to the postpartum period, and of continuous adjustments in nutrient metabolism and immune function. Fetal growth is regulated by balances between the fetus's demand for nutrients and the maternal–placental unit's supply. The timing of nutritional insults may induce specific alterations in both maternal reproductive health and embryonic/fetal development. Infancy is sensitive to both the quantity and the quality of the nutrient supply, which may affect a range of health outcomes in the short, medium, and long term. Milk, including breast milk, may be the only food an infant consumes for the first 6 months. Afterward, it must be adequately complemented with foods. The timely progression from a milk-based diet to complementary and family foods helps shape the offspring's health and eating environment. *Abbreviations*: CF, complementary feeding; IUGR, intrauterine growth restriction; LMP, last menstrual period; T, trimester.

maternal nutrition and metabolism, uteroplacental blood flow, and the size and transfer capabilities of the placenta.[3] Adjustments in the metabolism of nutrients evolve continuously, switching from an anabolic condition during early pregnancy to a catabolic one in late pregnancy.[3] Gestation-dependent immune adaptations also occur throughout pregnancy to ensure the capacity to adequately recognize and adapt defenses to specific pathogens. The immune cells and organs of the progeny proliferate in the first trimester and become mature in the late fetal and early neonatal periods. This delay in maturation of fetal defenses is countered by the uterine decidua, through which antimicrobial protection of mother and fetus is balanced with the need for immune tolerance to prevent fetal rejection.[4] Adequate maternal nutrition is crucial for fulfilling the increased energy and nutrient requirements to support fetal growth and to modulate both gut microbiota composition and functions such as gene expression, nervous system development, hormonal secretion, immune system maturation.[5–8]

Infancy is a complex period of rapid growth and development. Although the immune system is qualitatively complete at birth, exposures during infancy and early childhood are essential for priming the adaptive cell populations.[9] Furthermore, postnatally, the developing human brain, being functionally flexible, is very sensitive to external cues, which can shape structural/functional aspects of the brain as well as behavior.[10] Mounting evidence exists about associations between variations in infant feeding and health outcomes in both the short and the long term, with early growth acceleration linked to the early appearance of overweight and obesity.[11,12] For the first 6 months after birth, milk is the only food an infant should consume, with breast milk being the optimal form of nutrition for healthy infants.[13] Afterward, milk, even breast milk, alone is no longer sufficient to meet an infant's energy and nutrition requirements.[12] Besides meeting nutritional needs, the timely progression from a milk-based diet to one that includes complementary and family foods requires infants and toddlers to learn how to eat by achieving oral-motor abilities[14] and sensory experiences.[10]

The "developmental origins of health and disease" paradigm envisions health as being determined by early-life events in utero and infancy, when key regulatory systems are sensitive to immediate environmental exposures that permanently modify the body's structure, function, immune and metabolic phenotype, and, consequently, the risk of disease.[15] This implies a developmental plasticity through which alternative phenotypes are generated from a specific genotype by adjusting or adapting the developmental program in response to prevailing environmental cues. During different periods, human growth and the immune system demonstrate plasticity, which is modulated by energy resources, and the degree of plasticity may have markedly different implications for subsequent risks of morbidity, mortality, and reproductive fitness.[16]

Nutrition is one of the major environmental factors influencing pregnancy outcome and the growth trajectory of the fetus, with immediate and long-lasting effects on offspring health. The early life stages may represent an opportune time to influence an offspring's health and potential, not only by avoiding nutritional insults that have immediate adverse implications but also by establishing healthy eating habits that may be crucially important in preventing pediatric overweight/obesity, noncommunicable diseases, and micronutrient deficiencies, all of which have increased in prevalence worldwide.[17]

Overweight and obesity have pervasively increased in all age groups, resulting in immediate and long-term health risks.[18–20] It is alarming that at least 41 million children under the age of 5 years are overweight or obese, and overweight/obesity in females 10–24 years of age increased between 1990 and 2013, reaching a prevalence of nearly 1 in 5 young people in countries where noncommunicable diseases are predominant.[19] This poses a serious threat to health from childhood to adulthood.[19,21] In particular, maternal overweight and obesity lead to increased maternal morbidity and infant mortality, and pediatric obesity has become a major contributor to adult obesity, diabetes, and noncommunicable diseases.[20]

Noncommunicable diseases, comprising mainly cardiovascular disease, cancer, diabetes, and chronic lung disease, are the leading causes of mortality and morbidity globally.[22] The number of deaths due to noncommunicable diseases has increased from 27 million in 1990 to nearly 38 million in 2013,[23] with over 14 million deaths occurring in people between the ages of 30 and 70 years.[22] Rapid shifts in contemporary food patterns toward diets characterized by higher intakes of energy-dense, nutrient-poor foods and beverages, along with sedentary lifestyles, have likely contributed to an obesogenic environment.[24]

Micronutrient deficiencies are also widespread, mostly during infancy and pregnancy, because of the overall increased demand for nutrients.[25] Worldwide, the prevalence of iron-deficiency anemia among pregnant women is nearly 19%.[20] Undernutrition and deficiencies of vitamin A and zinc, along with suboptimal breastfeeding, are estimated to be responsible for nearly 3.1 million deaths of children under 5 years of age.[25] Worrisome is the coexistence of under- and overnutrition, ie, the so-called dual burden of malnutrition, as individuals may suffer overweight and obesity coupled with micronutrient deficiencies.[26]

At Expo Milano 2015, in Milan, Italy, leading experts discussed up-to-date knowledge about the conditioning of offspring health through the link between nutritional exposures occurring from conception to the postnatal period and the sensitive critical points involved in lifelong health (ie, epigenetics and the immune system), with a specific focus on dietary patterns, probiotics, vitamin D, and breastfeeding. Their goal was to highlight potential issues to be addressed in future research or translated into recommendations and to provide obstetricians, neonatologists, and pediatricians with specific aids to improve their skills in supporting patient care.

The main objective of this review, which reflects the authors' view, is to summarize the key topics critically debated in the conference concerning the cascade of effects and factors that determine the interplay between the nutritional environment from conception to early infancy and the offspring's lifelong health. First, environmentally sensitive critical points involved in lifelong health, that is, the potential health effects of changes in imprinted gene expression and microbiota determinants to environmental signals (ie, epigenetic mechanisms and immune system development/function, respectively) are discussed. Then, updated and relevant findings about associations between pre- and postnatal nutrition in terms of dietary patterns and components, probiotics, vitamin D, and infant feeding practices (ie, breastfeeding vs formula feeding) and the overall risks for reproductive outcomes and offspring morbidity are examined. Finally, the biological plausibility of the potential effect of early nutritional exposures on lifelong metabolic and allergic disease is discussed. In order to construct an objective and comprehensive picture about this issue, a broad array of studies are presented.

## CRITICAL ENVIRONMENTALLY SENSITIVE POINTS IN LIFELONG HEALTH

### Epigenetics during development: permanent effect of changes in imprinted gene expression on offspring health

Epigenetic mechanisms are responsible for the stable regulation of gene expression without changes to the

DNA sequence. They trigger initiation and/or maintenance of cell-type-specific transcriptional profiles by modulating the chromatin structure and by organizing the global 3-dimensional structure of the genome and nuclear architecture, thereby participating in the control of transcription.[27] Because of their dynamic nature, epigenetic mechanisms are sensitive to the environment, and the epigenome serves as an interface between the environment and the genome. Pollutants, nutrition, hormonal factors, and drugs may ultimately alter epigenetic landscapes during a particular spatiotemporal window in a tissue- and sex-specific manner.[2,28]

The methylation of DNA in the imprinted gene is one of the most studied epigenetic mechanisms implicated in the programming of cellular growth and the development of gametes, the embryo, and the fetus.[1,29] In comparison with their unexposed same-sex siblings, individuals who were periconceptionally exposed to famine had, 6 decades later, lower methylation of 5 CpG dinucleotides within the insulin-like growth factor-II differentially methylated region (DMR).[30] They also had higher methylation of loci within candidate genes involved in metabolic and cardiovascular disease, which differed depending on each individual's gender and gestational timing of exposure.[31] Likewise, the methylation status of specific CpGs from candidate genes in umbilical cord tissue DNA from healthy neonates was positively associated with a child's adiposity at age 9 years and was inversely associated with maternal carbohydrate intake in early pregnancy.[32] Children who were overweight/obese at 1 year of age had significantly higher methylation percentages at the *H19* DMR in cord blood leukocyte DNA at birth compared with nonobese children.[33]

### Immunological development in infancy and offspring health: host–microbe crosstalk from mother to newborn through pregnancy and caregiving

The gut microbiota is one of the early environmental factors that determine adult health. The antenatal composition of the microbiome at various time points and body sites is likely involved in immune and metabolic programming and probably influences the risk of gastrointestinal disease, allergy, autoimmune disease, and metabolic disorders in later life.[34]

The growing number of clinical conditions apparently linked to imbalance of the gut microbiota composition has fuelled clinical research interest in host–microbe crosstalk at early ages.[35,36] The main microbial exposure for the fetus, the neonate, and the infant is provided by the maternal microbiota in utero, during delivery, and via breastfeeding, whereby disturbances in the mother's microbiota composition and activity may not only immediately impact reproductive health but may also be transferred to the newborn (Figure 2). Recent scientific advances challenge traditional thinking that the human fetus is sterile, since microbe traces were detected in placenta, amniotic fluid, fetal membranes, and meconium.[37–39] Subsequent sources of bacteria include mammary glands through breastfeeding, the mother's skin and oral microbes, and the neonate's initial environment.[35] Several factors, combined with host influences, may modulate the dynamic composition of the mother–offspring microbiota interplay.[40] These include maternal weight[41–43] and diet,[7] mode of delivery,[43,44] environment,[45,46] medical interventions,[47] and feeding practices.[48,49]

The interaction of the gut microbiota composition with energy extracted from foods and storage in the human body suggests that the microbiome may be considered a proxy of nutritional status and/or a target for modulation. Overall, term infants delivered vaginally at home and breastfed exclusively seem to have the most beneficial gut microbiota,[50] whereas antibiotic treatment and cesarean delivery seem to promote suboptimal development of the microbiota in early infancy.[45]

## MATERNAL NUTRITION AND OFFSPRING HEALTH FROM CONCEPTION TO THE POSTNATAL PERIOD

When elucidating the potential effects of nutrition on reproductive outcomes, the composition of the diet, along with the intake of single foods and food compounds, must be examined, since health outcomes are endpoints for different conditions. Maternal weight status, lifestyle, and sociodemographic characteristics as well as and macroenvironmental factors may be important predictors of health concerns for both mother and child.

### Nurture at conception: the role of parental nutrition

Most reproductive failures originate during the periconceptional period and may be influenced by the age and lifestyle of the parents-to-be.[1] In particular, inadequate prepregnancy diets may impact the overall reproductive and/or pregnancy cycle.[5] For instance, increased adherence to dietary recommendations enhanced the chance of ongoing pregnancy in women undergoing in vitro fertilization treatment.[51] Moreover, a significantly increased risk of gestational diabetes mellitus was associated with high consumption of animal fats[52] or intake of a diet high in glycemic load or low in cereal fiber.[53]

Derangements in one-carbon metabolism driving both the synthesis of proteins, biogenic amines, and lipids necessary for growth and the methylation of DNA and histones essential for regulation of gene expression

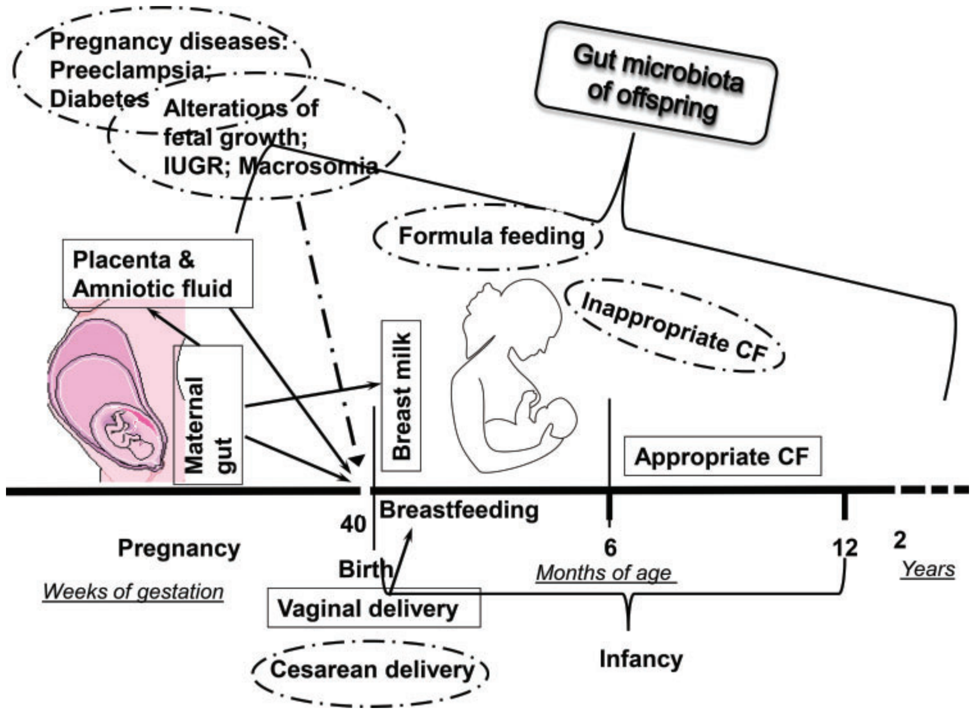


*Figure 2* **Microbial colonization of the offspring's gut: the stepwise routes from mother to infant.** The fetus comes into contact with microbes that originate in the maternal gut via the placenta and amniotic fluid. Afterward, transmission of bacteria from mother to newborn may occur through contact or transfer during birth (ie, vaginal delivery) and lactation. Breastfeeding, along with skin-to-skin contact and nursing, is also a source of maternal bacteria and modulates neonatal bacterial colonization and immune maturation. Disturbances in maternal microbiota composition and activity may be transferred to the infant by the same routes: during pregnancy, at birth, and after delivery. Maternal nutrition, pregnancy, obstetric and perinatal complications, formula feeding, and the environment may influence early microbial contact, intestinal colonization, and the subsequent risk of immune-mediated and metabolic disease in a detrimental manner (dotted lines). *Abbreviations*: CF, complementary feeding; IUGR, intrauterine growth restriction.

are linked to reproductive disorders in women and men and to poor pregnancy outcomes.[1] Malnutrition is recognized to disturb one-carbon metabolism, and, most importantly, poor nutrition around conception may enhance susceptibility to noncommunicable diseases. This increased susceptibility may be transmitted to succeeding generations, the underlying mechanisms of which may be explained by epigenetics.[15] New insights reveal that not only periconceptional maternal nutrition but also paternal nutrition may impact fertility and embryonic growth trajectories.[1,54]

## Nurture in utero: the role of maternal diet

Large prospective studies have demonstrated associations between the maternal diet during pregnancy and negative outcomes such as poor fetal growth trajectories, small for gestational age, inadequate length of gestation or preterm delivery, preeclampsia, and impaired glucose tolerance or gestational diabetes mellitus.

Healthy (traditional) dietary patterns such as the New Nordic Diet[55] and Mediterranean-type diets[56] were accompanied by fewer small-for-gestational-age infants, while a potential causal link between maternal intake of junk foods (ie, soft drinks, fast food, and/or processed meat and chips) and large-sized offspring has been identified.[57] The degree of adherence to a Mediterranean diet was positively associated not only with parameters of intrauterine size but also with plasma folate and serum vitamin $B_{12}$ concentrations and was inversely associated with uteroplacental vascular resistance, plasma homocysteine levels, and high-sensitivity C-reactive protein levels.[56] Inverse relationships were reported between adherence to a Mediterranean diet,[58] prudent and traditional diets,[59] and risk of preterm delivery.

Interesting results emerged when potential links to consumption of specific food item(s)/substances were explored. A lower risk of preterm delivery was found among women who met the recommendations for fish intake,[59] in agreement with a meta-analysis indicating that never consuming fish in pregnancy could be an extremely strong risk factor for preterm delivery.[60] Caffeine intake was consistently associated with lower birth weight and higher odds of small-for-gestational-age offspring, not only when consumption exceeded the World Health Organization's recommendation (300 mg/d) but also when it exceeded the recommendation in Nordic countries and the United States (maximum 200 mg/d), which suggests a risk of small-for-gestational-age infants even at very low intakes of caffeine.[61] In contrast to sugar-sweetened beverages, foods that naturally contain sugar, such as fresh and dried fruits, were inversely associated with the onset of preeclampsia, suggesting that, compared with foods containing industrially added sugars, foods with natural sugars contain other compounds such as dietary fiber that may be able to favorably modulate the influence of sugar on the onset of preeclampsia.[62] The consumption of probiotic milk products also seemed to play a beneficial role, mostly by preventing severe preeclampsia, with a lower risk observed even at moderate intakes (nearly 30 mL/d).[63] Additionally, daily consumption of 200 g of probiotic yogurt for 9 weeks was efficient in maintaining stable serum insulin levels among pregnant women in the third trimester, which indicates a preventive effect against insulin resistance.[64]

Diet quality appears to influence the risk of impaired glucose tolerance during pregnancy, too.[65] Impaired glucose tolerance late in pregnancy is not only associated with high intakes of saturated fat, *trans* fat, and added sugar and lower intakes of fiber[66] but is also significantly reduced by increasing carbohydrate vs fat intake[67] during the second trimester. This supports the idea that high-fat/low-carbohydrate diets early in pregnancy may result in a higher risk of gestational diabetes mellitus. Likewise, a Mediterranean diet is likely protective against the onset of gestational diabetes mellitus, as greater adherence is associated with better glucose tolerance and a lower incidence of gestational diabetes mellitus.[68]

A Mediterranean diet in pregnancy also seems to have a long-lasting protective influence against offspring allergies, while maternal consumption of olive oil, dairy products, and vitamin D may affect the risk of infantile wheeze and asthma, as shown in examples in Table 1.[69–75]

## Nurture in the postnatal period: the importance of breastfeeding

There is international consensus that infants should be breastfed exclusively for the first 6 months of life to achieve optimal growth, development, and health, with appropriate complementary foods introduced thereafter and breastfeeding continued for up to 2 years or beyond.[76] When the optimal 6 months of exclusive breastfeeding is not achievable, the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition recommends that "complementary foods should be introduced not earlier than 17 weeks of age and not later than 26 weeks."[77] Depending on the duration and amount of breastfeeding (exclusive vs partial), relationships between breastfeeding and a range of health outcomes in the short, medium, and long term have been observed.

*Eating behavior.* The type, timing, and duration of the milk-feeding regimen (breast vs formula) in early postnatal life may exert different effects on flavor learning and the establishment of food preferences, which appear to be long lived.[78] Prolonged breastfeeding may influence the initial acquisition of acceptance/preference of tastes and foods, facilitating the transition to adult foods.[79] In fact, breastfed children are likely more willing to try novel foods than formula-fed children.[80] Interestingly, greater exposure to breast milk is linked to healthier dietary patterns in both childhood[81,82] and adulthood.[83]

*Obesity.* Compared with formula feeding, breastfeeding seems to impart a protective effect against later obesity, despite complex and confounding relationships between early-life feeding practices and later risk of child obesity.[84,85] The issue has been recently questioned.[86] Overall, exclusive breastfeeding for longer than 4 months seems to be associated with lower weight gain and body mass index during age 6 to 12 months.[87] Infants breastfed from birth to 6 months of age gain weight, length, and adiposity more slowly and are of smaller size during infancy than those fed formula milk, independent of the timing of introducing solid foods.[88,89]

*Immune system.* Breastfeeding is likely associated with lower rates of overall infection up to 1 year of age. Breastfeeding exclusively for at least 4 months and continued partially thereafter seems to be protective against lower respiratory and gastrointestinal infections until the age of 6 months and against respiratory tract infections between the ages of 7 and 12 months.[90] During the first 6 months of life, exclusive breastfeeding is more protective against gastrointestinal infection than partial breastfeeding.[91] Protection against diarrhea and ear infections seems to be provided in a dose–response manner.[92] A positive association was also found between breastfeeding and reduced risk of asthma/wheezing in children with the probability of respiratory illness during childhood, with risk being significantly reduced in those breastfed exclusively for 15 weeks.[93]

*Table 1* **Relationship between offspring allergies early in life and maternal diet, food, and nutrient intake during pregnancy**

| Reference | Name, type, and country of study | Maternal dietary pattern | Outcome | Results |
|---|---|---|---|---|
| Chatzi et al. (2013)[69] | Multicenter INfancia y Medio Ambiente study (Spain) and RHEA study (Greece)<br>Meta-analysis | Mediterranean diet | Risk of wheeze and eczema in the first year of life | No association with adherence to Mediterranean diet<br>Increased risk of wheeze associated with high meat intake (RR = 1.22, 1.00–0.49) and processed-meat intake (RR = 1.18, 1.02–1.37)<br>Decreased risk of wheeze significantly associated with high intake of dairy products (RR = 0.83, 0.72–0.96) |
| Castro-Rodriguez et al. (2010)[70] | Part of the Estudio Internacional de Sibilancias en Lactantes<br>Birth cohort study<br>Spain | Mediterranean diet and olive oil for cooking/dressing salads | Wheezing during the first year of life | Olive oil intake associated with less wheezing (OR = 0.57, 0.4–0.9, $P = 0.002$) |
| Garcia-Marcos et al. (2013)[71] | Meta-analysis of studies, stratified into Mediterranean and non-Mediterranean centers | Mediterranean diet | Asthma prevalence in children | Current wheeze: negative association with the highest tertile of Mediterranean diet score : OR=0.85, 0.75–0.98, $P = 0.02$ (all centers); OR = 0.79, 0.66–0.94, $P = 0.009$ (Mediterranean centers)<br>Current severe wheeze: R = 0.82, 0.55–1.22, $P = 0.330$ (all); OR = 0.66, 0.48–0.90, $P = 0.008$ (Mediterranean centers)<br>Asthma: OR = 0.86, 0.78–0.95, $P = 0.004$ (all); OR = 0.86, 0.74–1.01, $P = 0.06$ (Mediterranean centers); OR = 0.86, 0.75–0.98, $P = 0.027$ (non-Mediterranean centers) |
| Sausenthaler et al. (2007)[72] | Influences of Lifestyle-related Factors on the Immune System and the Development of Allergies in Childhood Study<br>Prospective birth cohort study<br>Germany | Diet in the last 4 wk of pregnancy | Allergic sensitization and eczema at 2 y of age | Eczema: positive association with high intake of margarine (OR = 1. 49, 1.08–2.04), vegetable oils (OR = 1.48, 1.14–1.91); negative association with high fish intake (OR = 0.75, 0.57–0.98)<br>Sensitization against food allergens: increased risk with high celery intake (OR = 1.85, 1.18–2.89) or citrus fruit intake (OR = 1.73, 1.18–2.53)<br>Sensitization against inhalant allergens: positively related to a high intake of deep-fried vegetable fat (OR = 1.61, 1.02–2.54), raw sweet pepper (OR = 2.16, 1.20– 3.90), citrus fruit (OR = 1.72, 1.02–2.92) |
| Miyake et al. (2010)[73] | Osaka Maternal and Child Health Study<br>Prospective cohort study<br>Japan | Dairy products, calcium, and vitamin D | Risk of wheeze and eczema at 16–24 mo of age | Decreased risk of infantile wheeze related to higher intake of total dairy products (OR = 0.45, 0.25–0.79; $P = 0.007$), milk (OR = 0.50, 0.28–0.87; $P = 0.02$), cheese (OR = 0.51, 0.31–0.85; $P = 0.02$), calcium (OR = 0.57, 0.32–0.99; $P = 0.04$)<br>Categorization of vitamin D by cutoff at 25th percentile: significantly reduced risk of wheeze (OR = 0.64, 0.43–0.97), eczema (OR = 0.63, 0.41–0.98) |
| Errkola et al. (2009)[74] | Type 1 Diabetes Prediction and Prevention Study<br>Multidisciplinary, prospective, population-based cohort study<br>Finland | Vitamin D intake | Asthma, allergic rhinitis, atopic eczema by the age of 5 y | Mean intake = (5.1 ± 2.6) mg from food; (1.4 ± 2.6) mg from supplements<br>Vitamin D from food negatively related to asthma (HR = 0.80, 0.64–0.99; $P < 0.05$), AR (HR = 0.85, 0.75–0.97; $P < 0.05$) risk<br>Vitamin D supplements not associated |
| Camargo et al. (2007)[75] | Project Viva<br>Prospective prebirth cohort study<br>USA | Vitamin D intake | Risk of asthma in children at 3 y of age | Mean total intake = (548 ± 167) IU/d<br>Lowest quartile (median, 356 IU) vs highest quartile (724 IU): lower risk of recurrent wheeze (OR = 0.38, 0.22–0.65; $P < 0.001$).<br>100-IU increase associated with lower risk (OR = 0.81, 0.71–0.93), regardless of vitamin D source |

*Abbreviation*: HR, hazard ratio; IU, international units; MD, Mediterranean diet; OR odds ratio; RR, relative risk.

## POTENTIAL LINKS BETWEEN EARLY-LIFE NUTRITIONAL EXPOSURES AND LIFELONG METABOLIC AND ALLERGIC DISEASES

### Anti-inflammatory, antiatherogenic, immunomodulatory, and epigenetic factors of food compounds

The beneficial effects of healthy diets during pregnancy may be attributed to distinct dietary characteristics (ie, high intakes of fruits/vegetables, fish, whole-grain cereals, oils), which translate into the intake of beneficial compounds. Omega-3 polyunsaturated fatty acids from fish may have beneficial anti-inflammatory, antiatherogenic, and immunomodulatory effects.[94] Sources of dietary fiber, vitamins, minerals, and bioactive compounds – such as vegetables, fruits, oils, nuts, and whole grains – may exert protective effects by reducing inflammation, oxidative stress, and endothelial dysfunction and lowering low-density lipoprotein cholesterol and glycemic response.[95–97] Owing to their highly fermentable carbohydrate content, fruits, vegetables, and whole grains may also serve as prebiotic foods, which enhance the composition of the gut microbiota, implicated in the regulation of host energy homoeostasis and systemic/local immunity.[98,99]

Several of the aforementioned dietary components are also linked to epigenetic processes.[6] Indeed, nutrients and their metabolites may be direct activators or inhibitors of the epigenetic enzymes or substrates for membrane and nuclear receptors, leading to local chromatin changes at targeted gene sequences. In particular, folate, as a methyl-group donor in one-carbon metabolism, is involved in DNA methylation, together with vitamin $B_{12}$ and methionine.[100] Subtle variations in one-carbon metabolism genes and deficiencies in one-carbon substrates/cofactors, together with poor lifestyle, may provoke derangements in one-carbon metabolism, thereby compromising offspring health.[1] Periconceptional folic acid supplementation is internationally recommended for the prevention of neural tube defects.[101] However, high maternal levels of folate during pregnancy predicted higher adiposity and insulin resistance in offspring at age 6 years, whereas low levels of vitamin $B_{12}$ predicted higher insulin resistance,[102] and infants exposed to higher folic acid supplements later in pregnancy were more likely to develop eczema at 1 year of age than those born to mothers with lower intakes.[103] Epigenetic modifications of chromatin, ie, aberrant reprogramming of DNA methylation, may occur as a consequence of alterations in one-carbon metabolism.[1] Hoyo et al.[105] found that 17-month-old children of mothers who used periconceptional folic acid at 400 μg/d had a significantly higher methylation of insulin growth factor II-DMR than nonexposed children,[104] while methylation at the *H19* DMR in cord blood leukocytes was significantly lower in neonates of mothers who took periconceptional folic acid than in infants born to nonusers of folic acid.

### Vitamin D: specific importance in pregnancy and early life

Circulating concentrations of the hormonally active form of vitamin D [calcitriol, $1{,}25(OH)_2D$] are typically very tightly regulated. Despite this, serum concentrations in the expectant mother begin to rise early in the first trimester and double by the end of third trimester. Pregnancy-specific tissues, including the placenta and the decidua, also express hormonal vitamin D receptors. Both the placenta and the decidua have the capacity to synthesize CYP27B1, the key enzyme of vitamin D metabolism, providing further support for a specific role for vitamin D in pregnancy.[4]

Calcitriol elicits protective effects on vascular function by decreasing endothelial adhesion molecules and exerting anti-inflammatory activity. It also protects against inflammatory diseases and immune-mediated disorders by inhibiting adaptive immunity and enhancing innate immunity. Specifically, calcitriol inhibits the production of proinflammatory cytokines while promoting the emergence of regulatory T cells expressing proteins that mediate transplantation tolerance, strengthening the modulation of T-cell responses.[106]

The pro-tolerogenic effects of calcitriol at the maternofetal interface may contribute to the immunological adaptation by the mother, which is required for the maintenance of normal pregnancy. Furthermore, these immunomodulatory effects could also explain the reported association between vitamin D and a reduced risk of preeclampsia, for which evidence has been obtained from observational studies and clinical trials.[107]

The priming of the immune system occurs prenatally and during the first years of life, and therefore it is possible that the immunological effects of vitamin D could have longer-term influences for the offspring as well. In support of this hypothesis are studies reporting a protective association between vitamin D supplementation in infants and a reduced risk of type 1 diabetes.[108] A large number of studies have investigated the association between vitamin D and the subsequent risk of allergies and asthma, with prevention of deficiency and modest increases in vitamin D intakes typically suggesting a protective association.[73–75] However, there is also evidence to suggest that mothers with very high calcitriol concentrations or infants with high supplementation intakes may have an increased risk,[109,110] which is compatible with the suggested shift towards a

Th2-dominant immune-response pattern. The classical effect of calcitriol is the regulation of calcium metabolism and bone health, and observational data suggest that higher maternal vitamin D status is associated with a greater fetal femur volume and higher birth weight.[111] Randomized controlled trials of maternal vitamin D supplementation have provided evidence for beneficial effects on birth weight.[112]

Most vitamin D is obtained through endogenous synthesis by ultraviolet radiation after sun exposure of the skin, while typical diets are very low in vitamin D. The Institute of Medicine (United States) recommends 600 IU of vitamin D per day for expectant mothers and 400 IU per day for infants. Given that case reports suggest life-threatening implications for infants and children exposed to extreme vitamin D deficiency,[113] it is important to ensure adequate maternal and infant vitamin D intakes through supplementation, particularly in the absence of adequate exposure to sunlight and also because breast milk is very low in vitamin D.

## Impact of probiotic consumption on the immune system

Evidence accumulated so far suggests that modulating the microbiota composition by means of probiotics in the prenatal and early postnatal periods may counteract pregnancy complications and allergic/inflammatory conditions in offspring. Table 2 summarizes some of the clinical trials investigating the effects of perinatal oral administration of probiotic bacteria to pregnant women alone or to child–mother pairs.[114–120]

Administration of specific probiotics perinatally, namely in utero and/or in the first months of life (to lactating mothers and/or their infants), may promote healthy immune maturation and reduce allergies in the offspring. In fact, probiotic supplements administered in utero exerted a protective effect against sensitization in high-risk infants.[121] Moreover, the occurrence of eczema or chronically persistent eczema by the second year of age was significantly reduced both in at-risk infants of mothers given different mixtures of specific strains of lactobacilli/bifidobacteria during pregnancy and breastfeeding[117] and in infants supplemented pre- and postnatally with a combination of bifidobacteria.[116] Interestingly, maternal probiotic supplementation with *Lactobacillus rhamnosus* GG during pregnancy and lactation not only lowered the risk of atopic eczema in the first 2 years of life in the offspring but also increased the amount of transforming growth factor (TGF)-$\beta$2 in breast milk, thus augmenting breast milk's immune-protective potential.[118] On the other hand, no effect on atopic dermatitis and eczema was detected in infants 3- to 12-month-old with mild-to-moderate atopic dermatitis who were supplemented with *L. rhamnosus* GG[119] or in infants given, together with their mothers, pre- and postnatal supplementation with *Bifidobacterium animalis* subsp *lactis*.[120] Indeed, when the Committee on Nutrition of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition evaluated data about the health effects of formula supplemented with probiotics and/or prebiotics vs unsupplemented formula, evidence to recommend the routine use of probiotic-supplemented formula was deemed insufficient, despite some clinical benefits associated with a few probiotics added to infant or follow-on formulas and given beyond early infancy.[122] These conflicting results likely signify that the effects of probiotics are strain specific and that interventions are most effective if commenced during pregnancy.

Besides beneficially enhancing the composition of the gut microbiota, probiotics may restore increased intestinal permeability to normal, improve the intestine's immunological barrier function, and reduce the generation of proinflammatory cytokines.[46] Accordingly, maternal probiotic supplementation with *B. lactis* or *B. lactis* + *L. rhamnosus* GG significantly modulated the expression of Toll-like receptor (TLR)-related genes in both placenta and the fetal gut.[38] Probiotics also appear to beneficially influence glucose metabolism and weight gain in pregnant women.[114] Maternal supplementation with mixed lactobacilli/bifidobacteria from the first trimester of pregnancy to the end of exclusive breastfeeding resulted in a significant reduction in the risk of gestational diabetes mellitus as well as the risk of maternal central adiposity over the 12-month postpartum period.[115] Probiotics are postulated to be involved in the control of body weight and energy metabolism through modulation of both energy homeostasis and the low-grade inflammatory state that characterizes overweight/obesity and the onset of metabolic disorders such as insulin resistance and type 2 diabetes mellitus.[123]

On the basis of the currently available literature, pre-, peri-, and postnatal interventions with specific probiotic preparations may have potentially beneficial effects on child health and well-being. The safety of this approach in pregnancy has been proven by the normal duration of pregnancies, with neither adverse events in mothers or children nor significant variations in pre- or postnatal growth rates observed. Furthermore, no interference with the long-term composition or the quantity of gut microbiota has been reported. In particular, a targeted manipulation of gut microbiota seems to be an effective approach. However, it is worth noting that, owing to a lack of consistency across studies, to methodological limitations, and to data from single studies only, there is an urgent need for confirmatory, well-designed, adequately powered clinical research studies

Table 2 **Effects of perinatal probiotic supplementation on pregnancy, breast milk, and offspring**

| Reference | Population, study design | Probiotic | Outcome | Results |
|---|---|---|---|---|
| Dolatkhah et al. (2015)[114] | Pregnant women with GDM<br>RCT: probiotic vs placebo; 8-wk study period | *Lactobacillus (L.) acidophilus* LA-5 + *Bifidobacterium (B.)* BB-12 + *Streptococcus thermophilus* STY-31 + *L. delbrueckii bulgaricus* LBY-27 | Maternal glucose metabolism and weight changes | Significantly lower weight gain; significantly higher decrease in fasting blood sugar |
| Luoto et al. (2010)[115] | NAMI program: prospective, randomized mother–infant nutrition and probiotic study<br>Pregnant women; RCT: probiotic vs placebo; study period: from the first trimester | *L. rhamnosus* GG (LGG) (ATCC 53103) + *B. lactis* | GDM | Significantly reduced: 13% vs 36% |
| Enomoto et al. (2014)[116] | Pregnant women and their healthy infants Open trial: probiotic vs control; study period from 1 mo prior to delivery to 6 mo afterwards | *B. breve* M-16V + *B. longum* BB536 | Allergic diseases in offspring in the first 18 mo of age | Eczema/AD reduced at 10 mo (OR = 0.231, 0.084–0.628; $P = 0.007$) and 18 mo (OR = 0.304, 0.105–0.892; $P = 0.033$) |
| Rautava et al. (2012)[117] | Mothers with allergic disease and atopic sensitization<br>RCT: probiotic-1 vs probiotic-2 vs placebo; study period from 2 mo before delivery and during the first 2 mo of BF | Probiotic-1 = *L. rhamnosus* LPR + *B. longum* BL999 (LPR1BL999)<br>Probiotic-2 = *L. paracasei* ST11 + *B. longum* BL999 (ST111BL999) | Eczema in offspring during the first 24 mo of life | Eczema reduced: probiotic-1 = 0.17 (0.08–0.35), $P < 0.001$; probiotic-2 = 0.16 (0.08–0.35), $P < 0.001$<br>Chronically persistent eczema: probiotic-1 = 0.30 (0.12–0.80; $P = 0.016$); probiotic-2 = 0.17 (0.05–0.56; $P = 0.003$) |
| Rautava et al. (2002)[118] | Pregnant and lactating mothers, with and without atopic disease<br>RCT: probiotic vs placebo; study period from 4 wk before delivery and throughout BF | LGG (ATCC 53103) | Immunoprotective potential of breast milk; atopic eczema in offspring in the first 2 y of life | Eczema reduced: 15% vs 47%; RR = 0.32 (0.12–0.85), $P = 0.0098$<br>Breast milk TGF-$\beta$2: significantly higher |
| Grüber et al. (2007)[119] | Infants aged 3–12 mo with mild-to-moderate AD<br>RCT: probiotic vs placebo; 12-wk study period | LGG | Therapeutic effect on AD | No therapeutic effect with LGG in infants aged 3–12 mo with mild-to-moderate AD |
| Wickens et al. (2008)[120] | Child–mother pairs<br>RCT: probiotic-1 vs probiotic-2 vs placebo; study period from the wk 35 of gestation until 6 mo postpartum | Probiotic-1 = *L. rhamnosus*<br>Probiotic-2 = *B. animalis* subsp *lactis* | Eczema and atopy in offspring by 2 y of age | Probiotic-1: eczema reduced; HR = 0.51 (0.30–0.85), $P = 0.01$<br>Probiotic-2: no effect |

*Abbreviations*: AD, atopic dermatitis; BF, breastfeeding; GDM, gestational diabetes mellitus; NAMI, Nutrition, Allergy, Mucosal immunology and Intestinal; RCT, randomized control trial; TGF, transforming growth factor.

to establish the efficacy of supplemental probiotics and/or prebiotics in infant products.[122,124–126]

## Human milk: benefits beyond food and growth

Breastfeeding is acknowledged to be beneficial for infants, providing a balanced supply of nutrients, bioactive proteins, indigestible oligosaccharides, and bifidogenic bacteria.[85] Reflecting the pattern of development and maturation of the intestinal permeability and mucosal immune system of the infant, the biologically active components of human milk exhibit qualitative and quantitative changes during lactation that provide exogenous signals and components for gut ontogeny.[127,128]

Besides meeting the infant's increasing nutrient requirements, human milk primes the immune system and confers protection against pathogens. It transfers passive immune protection through products of the maternal adaptive immune system and its own innate immune system as well. The innate immune system of human milk comprises lactoferrin and lysozyme (involved in pathogen degradation), free fatty acids and monoglycerides (capable of destabilizing the cell membranes of pathogens), and glycans (able to inhibit binding of specific pathogens to intestinal epithelial receptors).[129] Breast milk contains compounds that modulate the gut microbiota composition by acting as prebiotics (ie, human milk oligosaccharides) and the developmental trajectory of the immune system (ie, anti-inflammatory cytokines such as the TGF-β2), thereby quenching proinflammatory processes and promoting immune tolerance.[35,129] It supplies probiotic bacteria, which colonize the infant's gut, beneficially modify the gut microbiota composition, and contribute to the reduced incidence/severity of infection and the maturation of infant immune system.[130] Human milk accelerates maturation of the gut barrier function through human milk oligosaccharides that were shown ex vivo to attenuate pathogen-associated molecular pattern (PAMP)-stimulated acute-phase inflammatory cytokine proteins while stimulating expression of cytokines involved in tissue repair and homeostasis[128], and enhancing in vitro epithelial cell kinetics and function.[131] When formula-fed and breastfed infants were compared, breastfed infants exhibited significantly higher levels of TGF-$\beta$2 and lower levels of the proinflammatory cytokines tumor necrosis factor-$\alpha$ and interleukin 2 throughout the first year of life and beyond the duration of breastfeeding.[132] Moreover, striking differences in gut microbiota composition were found, with bifidobacteria dominating in breastfed infants and *Bacteroides* species, *Clostridium coccoides*, and *Lactobacillus* species predominating in formula-fed infants.[45]

The preventive effects of breast milk against obesity and metabolic disorders in childhood and beyond likely depend on several growth factors and peptide/protein hormones that play roles in the regulation of appetite and food intake, energy balance, growth patterns, body composition, and glucose homeostasis early in infancy.

There are remarkable differences between formula-fed and breastfed infants. As a consequence of both the breast milk composition and the way an infant feeds at the breast, breastfed infants are believed to better regulate their food intake.[133] Changes in ghrelin, leptin, and fat levels in foremilk and hindmilk, which do not occur in formula milk, may explain the association of human milk with the infant's self-control of feeding.[134] A significantly higher percentage of weight gain has been found in formula-fed infants compared with both exclusively breastfed and partially breastfed infants, probably stimulated by a different pattern of the insulin growth factor axis.[135] The lower protein content of breast milk compared with formula milk is associated with a decreased weight-gain velocity.[136] Interestingly, breastfeeding is related to greater appetite regulation than bottle-feeding, regardless of the type of milk. When investigating whether feeding mode (bottle vs breast) and type of milk in the bottle (formula vs expressed breast milk) in the first 6 months of age influenced a child's later eating behavior, infants fed breast milk in a bottle exhibited both a higher consumption of milk in the second 6 months [137] and a lower satiety responsiveness at 3to 6 years of age[138] than those directly breastfed.

These findings suggest that breastfeeding itself, rather than breast milk, is related to greater appetite regulation, which highlights the importance of maternal–infant bonding in infants' eating behavior.[139] Through breastfeeding, mothers learn to become responsive, namely to recognize the infant's signals of hunger and satiety, thus feeding or stopping accordingly, and to develop a feeding style that is less controlling, thus allowing infants to maintain their natural ability to regulate energy intake, with long-lasting effects on complementary feeding.[140] In contrast, bottle feeding may provide misleading visual cues, leading mothers or caregivers to feed in response to amounts in the bottle rather than responsively to the infant's cues.

## CONCLUSION

In recent years, there has been increased awareness that interactions between pre- and postnatal environmental nutrition may ultimately determine offspring health.[17] The current obesogenic environment, which compromises the nutrient supply by providing foods with a low nutrient density as the major contributors to total energy, carbohydrate, and fat intakes, is potentially of concern because some pregnancy-related diseases are linked to the offspring's growth trajectory and to gene–epigenome variations implicated in the developmental origins of health and disease. Reducing the prevalence of malnutrition and its consequences is of great importance for public health. Therefore, a consistent translation of research results into nutrition recommendations and policy endorsements needs to be achieved. Education and translational research to support the adoption of a healthy lifestyle from the periconceptional period onward, if integrated into patient care, may have important implications for the prevention of short-term adverse reproductive outcomes and long-term health. This may offer substantial benefits for the health of current and succeeding generations, ultimately leading to healthcare and societal cost savings. Emergent findings show that not only maternal but also paternal nutrition is crucial for optimal conception, pregnancy, and lifelong health of the offspring

Personalized interventions to improve parental nutrition should be implemented right at the start of a new life. Indeed, individuals are much more likely to be motivated to improve their nutrition and lifestyle behaviors during the vulnerable reproductive period, because of the immediate benefit of having a healthy child.[141] Most of the findings about in utero nutrition, despite being observational, highlight the importance of diet composition for both pregnancy and the long-term health of mother and child, including ramifications for the gut flora and the body's immune response.

As practical recommendations, pregnant women should be encouraged to eat a balanced diet and to lower their consumption of sugar-sweetened beverages and processed meats, as suggested by current national and international dietary guidelines, and should consume 200 g of fatty fish per week to reach the recommended intake of n-3 long-chain polyunsaturated fatty acids while remaining below the tolerable upper intake for contaminants.[142] There is evidence to suggest that maternal vitamin D status may have important short- and long-term influences on both a pregnant woman's health and the health of her offspring. The diet is typically a very poor source of vitamin D; hence, in the absence of adequate sunlight-induced vitamin D synthesis, supplementation may be required.

The gut plays a central role in the ontogenic development of immune tolerance, and a well-balanced microbial composition in utero through infancy is pivotal for the establishment of immune homeostasis later in life. Overall, term infants born vaginally and breastfed exclusively have the most beneficial gut microbiota, while antibiotic treatment and cesarean delivery promote suboptimal development of the microbiota in early infancy. Specific probiotics have been reported to modulate immune responses. Experimental trials seem to indicate the potential for supplementation with probiotics (or probiotic-containing foods such as yogurt) and/or prebiotics (or prebiotic-containing-foods) during pregnancy and breastfeeding as a safe and effective strategy to prevent certain complications of pregnancy and to enhance the immune-protective potential of breast milk, perhaps reducing allergic/inflammatory conditions in offspring. In its guidelines for prevention of allergic disease, the World Allergy Organization recommends the use of probiotics in pregnant women at high risk of having an allergic child; in women who breastfeed infants at high risk of developing allergy; and in infants at high risk of developing allergy, albeit conditionally.[126] Indeed, each probiotic strain is inherently unique, and similar health effects cannot be expected even from closely related strains. Overall, recommendations and guidelines for treatment interventions should be meticulously defined.[143] For probiotics, it is important to characterize each probiotic to the species and strain level and to select strains with documented properties, as the probiotic potential is strain specific.[126,144] It is also important to document preclinical effects by means of markers relevant to the clinical condition in question. This means that further well-powered and carefully conducted clinical trials with long-term follow-up are needed.[145]

Breastfeeding is strongly recognized as a healthy behavior with many short- and long-term benefits for mother and infant, including the facilitation of mother–infant bonding.[146] To promote and support breastfeeding, neonatologists and pediatricians need specific knowledge and skills. In maternity hospitals and neonatal units, appropriate organizational interventions to facilitate the initiation of breastfeeding and the use of mother's/human milk should be implemented.[147] Hence, all maternity units should be encouraged to implement significant strategies and practical changes to achieve accreditation as a United Nations Children's Fund/World Health Organization Baby-Friendly Hospital by complying with the Ten Steps to Successful Breastfeeding, which may represent an effective strategy to increase both the rates of breastfeeding initiation and the duration of breastfeeding.[148]

## Acknowledgments

The authors are grateful to Sabino Maria Frassà, General Director of the Giorgio Pardi Foundation, and Ama Nutri Cresci for having conceived and directed the international scientific congresses at Expo Milano 2015. They also thank the Giorgio Pardi Foundation and Ama Nutri Cresci for overall support.

*Funding/support*. This research was partially funded by the Giorgio Pardi Foundation. The funder had no role in the development, preparation, or review of the manuscript.

*Declaration of interest*. The authors have no relevant interests to declare.

## REFERENCES

1. Steegers-Theunissen RPM, Twigt J, Pestinger V, et al. The periconceptional period, reproduction and long-term health of offspring: the importance of one-carbon metabolism. Hum Reprod Update. 2013;19:640–655.
2. Tarrade A, Panchenko P, Junien C, et al. Placental contribution to nutritional programming of health and diseases: epigenetics and sexual dimorphism. J Exp Biol. 2015;218(pt 1):50–58.
3. Berti C, Decsi T, Dykes F, et al. Critical issues in setting micronutrient recommendations for pregnant women: an insight. Matern Child Nutr. 2010;6(suppl 2):5S–22S.
4. Tamblyn JA, Hewison M, Wagner CL, et al. Immunological role of vitamin D at the maternal–fetal interface. J Endocrinol. 2015;224:R107–R121.
5. Cetin I, Berti C, Calabrese S. Role of micronutrients in the periconceptional period. Hum Reprod Update. 2010;16:80–95.
6. Palmer DJ, Huang R-C, Craig JM, et al. Nutritional influences on epigenetic programming: asthma, allergy, and obesity. Immunol Allergy Clin North Am. 2014;34:825–837.
7. Collado MC, Cernada M, Bäuerl C, et al. Microbial ecology and host-microbiota interactions during early life stages. Gut Microbes. 2012;3:352–365.
8. Berti C, Cetin I, Agostoni C, et al. Pregnancy and infants' outcome: nutritional and metabolic implications. Crit Rev Food Sci Nutr. 2016;56:82–91.
9. Renz H, Brandtzaeg P, Hornef M. The impact of perinatal immune development on mucosal homeostasis and chronic inflammation. Nat Rev Immunol. 2011;12:9–23.
10. Ventura AK, Worobey J. Early influences on the development of food review preferences. Curr Biol. 2013;23:R401–R408.

11. Young BE, Johnson SL, Krebs NF. Biological determinants linking infant weight gain and child obesity: current knowledge and future directions. Adv Nutr. 2012;3:675–686.
12. Agostoni C, Baselli L, Mazzoni MB. Early nutrition patterns and diseases of adulthood: a plausible link? Eur J Intern Med. 2013;24:5–10.
13. Jeurink PV, van Bergenhenegouwen J, Jiménez E, et al. Human milk: a source of more life than we imagine. Benef Microbes. 2013;4:17–30.
14. Delaney AL, Arvedson JC. Development of swallowing and feeding: prenatal through first year of life. Dev Disabil Res Rev. 2008;14:105–117.
15. Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol Rev. 2014;94:1027–1076.
16. Hochberg Z, Feil R, Constancia M, et al. Child health, developmental plasticity, and epigenetic programming. Endocr Rev. 2011;32:159–224.
17. Hanson MA, Bardsley A, De-Regil LM, et al. The International Federation of Gynecology and Obstetrics (FIGO) recommendations on adolescent, preconception, and maternal nutrition: "Think Nutrition First". Int J Gynaecol Obstet. 2015;131(suppl 4):S213–S253.
18. Lassi ZS, Bhutta ZA. Risk factors and interventions related to maternal and prepregnancy obesity, prediabetes and diabetes for maternal, fetal and neonatal outcomes: a systematic review. Expert Rev Obstet Gynecol. 2013;8:639–660.
19. Patton GC, Sawyer SM, Santelli JS, et al. Our future: a Lancet commission on adolescent health and wellbeing. Lancet. 2016;387:2423–2478.
20. Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 2013;382:427–451.
21. Nishtar S, Gluckman P, Armstrong T. Ending childhood obesity: a time for action. Lancet. 2016;387:825–827.
22. World Health Organization. Noncommunicable Diseases – Country Profiles (2014). http://apps.who.int/iris/bitstream/10665/128038/1/9789241507509_eng.pdf. Published (2014). Accessed September 26, (2016).
23. Naghavi M, Wang H, Lozano R, et al. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study (2013). Lancet. 2015;385:117–171.
24. Malik VS, Willett WC, Hu FB. Global obesity: trends, risk factors and policy implications. Nat Rev Endocrinol. 2013;9:13–27.
25. Bhutta ZA, Das JK, Rizvi A, et al. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet. 2013;382:452–477.
26. Tzioumis E, Adair LS. Childhood dual burden of under- and overnutrition in low-and middle-income countries: a critical review. Food Nutr Bull. 2014;35:230–243.
27. Attig L, Gabory A, Junien C. Modern approaches to nutritional research challenges nutritional developmental epigenomics: immediate and long-lasting effects. Proc Nutr Soc. 2010;69:221–231.
28. Hogg K, Price EM, Hanna CW, et al. Prenatal and perinatal environmental influences on the human fetal and placental epigenome. Clin Pharmacol Ther. 2012;92:716–726.
29. Choi S-W, Friso S. Epigenetics: a new bridge between nutrition and health. Adv Nutr. 2010;1:8–16.
30. Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A. 2008;105:17046–17049.
31. Tobi EW, Lumey LH, Talens RP, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. Hum Mol Genet. 2009;18:4046–4053.
32. Godfrey K.M, Sheppard A, Gluckman PD, et al. Epigenetic gene promoter methylation at birth is associated with child's later adiposity. Diabetes. 2011;60:1528–1534.
33. Perkins E, Murphy SK, Murtha AP, et al. Insulin-like growth factor 2/H19 methylation at birth and risk of overweight and obesity in children. J Pediatr. 2012;161:31–39.
34. Kerr CA, Grice DM, Tran CD, et al. Early life events influence whole-of-life metabolic health via gut microflora and gut permeability. Crit Rev Microbiol. 2015;41:326–340.
35. Rautava S, Luoto R, Salminen S, et al. Microbial contact during pregnancy, intestinal colonization and human disease. Nat Rev Gastroenterol Hepatol. 2012;9:565–576.
36. Reid G, Brigidi P, Burton JP, et al. Microbes central to human reproduction. Am J Reprod Immunol. 2015;73:1–11.
37. Jiménez E, Marín ML, Martín R, et al. Is meconium from healthy newborns actually sterile? Res Microbiol. 2008;159:187–193.
38. Rautava S, Collado MC, Salminen S, et al. Probiotics modulate host-microbe interaction in the placenta and fetal gut: a randomized, double-blind, placebo-controlled trial. Neonatology. 2012;102:178–184.
39. Aagaard K, Ma J, Antony KM, et al. The placenta harbors a unique microbiome. Sci Transl Med. 2014;6:237ra65. doi:10.1126/scitranslmed.3008599.
40. Chilton SN, Enos MK, Burton JP, et al. The effects of diet and the microbiome on reproduction and longevity: a comparative review across 5 continents. J Nutr Food Sci. 2015;5:364. doi:10.4172/2155-9600.1000364.
41. Collado MC, Isolauri E, Laitinen K, et al. Effect of mother's weight on infant's microbiota acquisition, composition, and activity during early infancy: a prospective follow-up study initiated in early pregnancy. Am J Clin Nutr. 2010;92:1023–1030.
42. Santacruz A, Collado MC, García-Valdés L, et al. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. Br J Nutr. 2010;104:83–92.
43. Cabrera-Rubio R, Collado MC, Laitinen K, et al. The human milk microbiome changes over lactation and is shaped by maternal weight and mode of delivery. Am J Clin Nutr. 2012;96:544–551.
44. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A. 2010;107:11971–11975.
45. Fallani M, Young D, Scott J, et al. Intestinal microbiota of 6-week-old infants across Europe: geographic influence beyond delivery mode, breastfeeding, and antibiotics. J Pediatr Gastroenterol Nutr. 2010;51:77–84.
46. Reid JNS, Bisanz JE, Monachese M, et al. The rationale for probiotics improving reproductive health and pregnancy outcome. Am J Reprod Immunol. 2013;69:558–566.
47. Eggesbø M, Moen B, Peddada S, et al. Development of gut microbiota in infants not exposed to medical interventions. APMIS. 2011;119:17–35.
48. Adlerberth I, Wold AE. Establishment of the gut microbiota in Western infants. Acta Pædiatr. 2009;98:229–238.
49. De Filippo C, Cavalieri D, Di Paola M, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci U S A. 2010;107:14691–14696.
50. Penders J, Stobberingh EE, Thijs C, et al. Molecular fingerprinting of the intestinal microbiota of infants in whom atopic eczema was or was not developing. Clin Exp Allergy. 2006;36:1602–1608.
51. Twigt JM, Bolhuis ME, Steegers EA, et al. The preconception diet is associated with the chance of ongoing pregnancy in women undergoing IVF/ICSI treatment. Hum Reprod. 2012;27:2526–2531.
52. Bowers K, Tobias DK, Yeung E, et al. A prospective study of prepregnancy dietary fat intake and risk of gestational diabetes. Am J Clin Nutr. 2012;95:446–453.
53. Zhang C, Liu S, Solomon CG, et al. Dietary fiber intake, dietary glycemic load, and the risk for gestational diabetes mellitus. Diabetes Care. 2006;29:2223–2230.
54. Hocher B. More than genes: the advanced fetal programming hypothesis. J Reprod Immunol. 2014;104–105:8–11.
55. Hillesund ER, Bere E, Haugen M, et al. Development of a New Nordic Diet score and its association with gestational weight gain and fetal growth – a study performed in the Norwegian Mother and Child Cohort Study (MoBa). Public Health Nutr. 2014;17:1909–1918.
56. Timmermans S, Steegers-Theunissen RP, Vujkovic M, et al. The Mediterranean diet and fetal size parameters: the Generation R Study. Br J Nutr. 2012;108:1399–1409.
57. Wen LM, Simpson JM, Rissel C, et al. Maternal "junk food" diet during pregnancy as a predictor of high birthweight: findings from the Healthy Beginnings Trial. Birth. 2013;40:46–51.
58. Mikkelsen TB, Osterdal ML, Knudsen VK, et al. Association between a Mediterranean-type diet and risk of preterm birth among Danish women: a prospective cohort study. Acta Obstet Gynecol Scand. 2008;87:325–330.
59. Haugen M, Meltzer HM, Brantsaeter AL, et al. Mediterranean-type diet and risk of preterm birth among women in the Norwegian Mother and Child Cohort Study (MoBa): a prospective cohort study. Acta Obstet Gynecol Scand. 2008;87:319–324.
60. Leventakou V, Roumeliotaki T, Martinez D, et al. Fish intake during pregnancy, fetal growth, and gestational length in 19 European birth cohort studies. Am J Clin Nutr. 2014;99:506–516.
61. Sengpiel V, Elind E, Bacelis J, et al. Maternal caffeine intake during pregnancy is associated with birth weight but not with gestational length: results from a large prospective observational cohort study. BMC Med. 2013;11:42. doi:10.1186/1741-7015-11-42.
62. Borgen I, Aamodt G, Harsem N, et al. Maternal sugar consumption and risk of preeclampsia in nulliparous Norwegian women. Eur J Clin Nutr. 2012;66:920–925.
63. Brantsaeter AL, Myhre R, Haugen M, et al. Intake of probiotic food and risk of preeclampsia in primiparous women: the Norwegian Mother and Child Cohort Study. Am J Epidemiol. 2011;174:807–815.
64. Asemi Z, Samimi M, Tabassi Z, et al. Effect of daily consumption of probiotic yoghurt on insulin resistance in pregnant women: a randomized controlled trial. Eur J Clin Nutr. 2013;67:71–74.
65. Louie JC, Brand-Miller JC, Markovic TP, et al. Glycemic index and pregnancy: a systematic literature review. J Nutr Metab. 2010;(2010):282464. doi:10.1155/(2010)/282464.
66. Ley SH, Hanley AJ, Retnakaran R, et al. Effect of macronutrient intake during the second trimester on glucose metabolism later in pregnancy. Am J Clin Nutr. 2011;94:1232–1240.
67. Saldana TM, Siega-Riz AM, Adair LS. Effect of macronutrient intake on the development of glucose intolerance during pregnancy. Am J Clin Nutr. 2004;79:479–486.

68. Karamanos B, Thanopoulou A, Anastasiou E, et al. Relation of the Mediterranean diet with the incidence of gestational diabetes. Eur J Clin Nutr. 2014;68:8–13.
69. Chatzi L, Garcia R, Roumeliotaki T, et al. Mediterranean diet adherence during pregnancy and risk of wheeze and eczema in the first year of life: INMA (Spain) and RHEA (Greece) mother–child cohort studies. Br J Nutr. 2013;110:2058–2068.
70. Castro-Rodriguez JA, Garcia-Marcos L, Sanchez-Solis M, et al. Olive oil during pregnancy is associated with reduced wheezing during the first year of life of the offspring. Pediatr Pulmonol. 2010;45:395–402.
71. Garcia-Marcos L, Castro-Rodriguez JA, Weinmayr G, et al. Influence of Mediterranean diet on asthma in children: a systematic review and meta-analysis. Pediatr Allergy Immunol. 2013;24:330–338.
72. Sausenthaler S, Koletzko S, Schaaf B, et al. Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age. Am J Clin Nutr. 2007;85:530–537.
73. Miyake Y, Sasaki S, Tanaka K, et al. Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants. Eur Respir J. 2010;35:1228–1234.
74. Erkkola M, Kaila M, Nwaru BI, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. Clin Exp Allergy. 2009;39:875–882.
75. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. Am J Clin Nutr. 2007;85:788–795.
76. World Health Organization. The Optimal Duration of Exclusive Breastfeeding: Report of an Expert Consultation. http://www.who.int/nutrition/publications/optimal_duration_of_exc_bfeeding_report_eng.pdf. Published (2002). Accessed February 26, (2016).
77. Agostoni C, Decsi T, Fewtrell M, et al. Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2008;46:99–110.
78. Beauchamp GK, Mennella JA. Early flavor learning and its impact on later feeding behavior. Pediatr Gastroenterol Nutr. 2009;48(suppl 1):S25–S30.
79. Schwartz C, Chabanet C, Laval C, et al. Breast-feeding duration: influence on taste acceptance over the first year of life. Br J Nutr. 2013;109:1154–1161.
80. Mennella J. Ontogeny of taste preferences: basic biology and implications for health. Am J Clin Nutr. 2014;99:704S–711S.
81. de Lauzon-Guillain B, Jones L, Oliveira A, et al. The influence of early feeding practices on fruit and vegetable intake among preschool children in 4 European birth cohorts. Am J Clin Nutr. 2013;98:804–812.
82. Robinson S, Ntani G, Simmonds S, et al. Type of milk feeding in infancy and health behaviours in adult life: findings from the Hertfordshire Cohort Study. Br J Nutr. 2013;109:1114–1122.
83. Scott JA, Chih TY, Oddy WH. Food variety at 2 years of age is related to duration of breastfeeding. Nutrients. 2012;4:1464–1474.
84. Farrow C, Haycraft E, Mitchell G. Milk feeding, solid feeding, and obesity risk: a review of the relationships between early life feeding practices and later adiposity. Curr Obes Rep. 2013;2:58–64.
85. Dieterich CM, Felice JP, O'Sullivan E, et al. Breastfeeding and health outcomes for the mother-infant dyad. Pediatr Clin N Am. 2013;60:31–48.
86. Casazza K, Fontaine KR, Astrup A, et al. Myths, presumptions, and facts about obesity. N Engl J Med. 2013;368:446–454.
87. Hörnell A, Lagström H, Lande B, et al. Breastfeeding, introduction of other foods and effects on health: a systematic literature review for the 5th Nordic Nutrition Recommendations. Food Nutr Res. 2013;57. doi:10.3402/fnr.v57i0.20823.
88. Baird J, Poole J, Robinson S, et al. Milk feeding and dietary patterns predict weight and fat gains in infancy. Paediatr Perinat Epidemiol. 2008;22:575–586.
89. Moorcroft KE, Marshall JL, McCormick FM. Association between timing of introducing solid foods and obesity in infancy and childhood: a systematic review. Matern Child Nutr. 2011;7:3–26.
90. Duijts L, Jaddoe VW, Hofman A, et al. Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy. Pediatrics. 2010;126:e18–e25.
91. Kramer MS, Guo T, Platt RW, et al. Infant growth and health outcomes associated with 3 compared with 6 mo of exclusive breastfeeding. Am J Clin Nutr. 2003;78:291–295.
92. Scariati PD, Grummer-Strawn LM, Fein SB. A longitudinal analysis of infant morbidity and the extent of breastfeeding in the United States. Pediatrics. 1997;99:e1–e5.
93. Dogaru CM, Nyffenegger D, Pescatore AM, et al. Breastfeeding and childhood asthma: systematic review and meta-analysis. Am J Epidemiol. 2014;179:1153–1167.
94. Calder PC, Kremmyda L-S, Vlachava M, et al. Early programming of the immune system and the role of nutrition. Is there a role for fatty acids in early life programming of the immune system? Proc Nutr Soc. 2010;69:373–380.
95. Fardet A. New hypotheses for the health-protective mechanisms of whole-grain cereals: what is beyond fibre? Nutr Res Rev. 2010;23:65–134.
96. Casas R, Emilio Sacanella E, Estruch R. The immune protective effect of the Mediterranean diet against chronic low-grade inflammatory diseases. Endocr Metab Immune Disord Drug Targets. 2014;14:245–254.
97. Del Chierico F, Vernocchi P, Dallapiccola B, et al. Mediterranean diet and health: food effects on gut microbiota and disease control. Int J Mol Sci. 2014;15:11678–11699.
98. Lomax AR, Calder PC. Prebiotics, immune function, infection and inflammation: a review of the evidence. Br J Nutr. 2009;101:633–658.
99. Delzenne NM, Neyrinck AM, Cani PD. Gut microbiota and metabolic disorders: how prebiotic can work? Br J Nutr. 2013;109(suppl 2):S81–S85.
100. Anderson OS, Sant KE, Dolinoy DC. Nutrition and epigenetics: an interplay of dietary methyl donors, one-carbon metabolism, and DNA methylation. J Nutr Biochem. 2012;23:853–859.
101. Berti C, Biesalski HK, Gärtner R, et al. Micronutrients in pregnancy: current knowledge and unresolved questions. Clin Nutr. 2011;30: 689–701.
102. Yajnik CS, Deshpande SS, Jackson AA, et al. Vitamin $B_{12}$ and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study. Diabetologia. 2008;51:29–38.
103. Dunstan JA, West C, McCarthy S, et al. The relationship between maternal folate status in pregnancy, cord blood folate levels, and allergic outcomes in early childhood. Allergy. 2012;67:50–57.
104. 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. doi:10.1371/journal.pone.0007845.
105. Hoyo C, Murtha AP, Schildkraut JM, et al. Methylation variation at *IGF2* differentially methylated regions and maternal folic acid use before and during pregnancy. Epigenetics. 2011;7: 928–936.
106. Hewison M. An update on vitamin D and human immunity. Clin Endocrinol. 2012;76:315–325.
107. Hyppönen E, Cavadino A, Williams D, et al. Vitamin D and pre-eclampsia: original data, systematic review and meta-analysis. Ann Nutr Metab. 2013;63:331–340.
108. Hyppönen E. Vitamin D and increasing incidence of type 1 diabetes – evidence for an association? Diabetes Obes Metab. 2010;12:737–743.
109. Hyppönen E, Sovio U, Wjst M, et al. Infant vitamin D supplementation and allergic conditions in adulthood Northern Finland Birth Cohort (1966). Ann N Y Acad Sci. 2004;1037:84–95.
110. Weisse K, Winkler S, Hirche F, et al. Maternal and newborn vitamin D status and its impact on food allergy development in the German LINA cohort study. Allergy. 2013;68:220–228.
111. Ioannou C, Javaid MK, Mahon P, et al. The effect of maternal vitamin D concentration on fetal bone. J Clin Endocrinol Metab. 2012;97:E2070–E2077.
112. Theodoratou E, Tzoulaki I, Zgaga L, et al. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ. 2014;348:g2035. doi:10.1136/bmj.g2035.
113. Scheimberg I, Perry L. Does low vitamin D have a role in pediatric morbidity and mortality? An observational study of vitamin D in a cohort of 52 postmortem examinations. Pediatr Devel Pathol. 2014;17:455–464.
114. Dolatkhah N, Hajifaraji M, Abbasalizadeh F, et al. Is there a value for probiotic supplements in gestational diabetes mellitus? A randomized clinical trial. J Health Popul Nutr. 2015;33:25. doi:10.1186/s41043-015-0034-9.
115. Luoto R, Laitinen K, Nermes M, et al. Impact of maternal probiotic-supplemented dietary counseling on pregnancy outcome and prenatal and postnatal growth: a double-blind, placebo-controlled study. Br J Nutr. 2010;103:1792–1799.
116. Enomoto T, Sowa M, Nishimori K, et al. Effects of bifidobacterial supplementation to pregnant women and infants in the prevention of allergy development in infants and on fecal microbiota. Allergol Int. 2014;63:575–585.
117. Rautava S, Kainonen E, Salminen S, et al. Maternal probiotic supplementation during pregnancy and breast-feeding reduces the risk of eczema in the infant. J Allergy Clin Immunol. 2012;130:1355–1360.
118. Rautava S, Kalliomäki M, Isolauri E. Probiotics during pregnancy and breastfeeding might confer immunomodulatory protection against atopic disease in the infant. J Allergy Clin Immunol. 2002;109:119–121.
119. Grüber C, Wendt M, Sulser C, et al. Randomized, placebo-controlled trial of *Lactobacillus rhamnosus* GG as treatment of atopic dermatitis in infancy. Allergy. 2007;62:1270–1276.
120. Wickens K, Black PN, Stanley TV, et al. A differential effect of 2 probiotics in the prevention of eczema and atopy: a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol. 2008;122:788–794.
121. Huurre A, Laitinen K, Rautava S, et al. Impact of maternal atopy and probiotic supplementation during pregnancy on infant sensitization: a double-blind placebo-controlled study. Clin Exp Allergy. 2008;38:1342–1348.
122. Braegger C, Chmielewska A, Decsi T, et al. Supplementation of infant formula with probiotics and/or prebiotics: a systematic review and comment by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2011;52:238–250.
123. Moreno-Indias I, Cardona F, Tinahones FJ, et al. Impact of the gut microbiota on the development of obesity and type 2 diabetes mellitus. Front Microbiol. 2014;5:190. doi:10.3389/fmicb.(2014).00190.

124. Thomas DW, Greer FR, American Academy of Pediatrics Committee on Nutrition, Section on Gastroenterology, Hepatology, and Nutrition. Probiotics and prebiotics in pediatrics. Pediatrics. 2010;126:1217–1231.
125. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific Opinion on the essential composition of infant and follow-on formulae. EFSA J. 2014;12:3760. doi:10.2903/j.efsa.(2014).3760.
126. Fiocchi A, Pawankar R, Cuello-Garcia C, et al. World Allergy Organization–McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics. World Allergy Organ J. 2015;8:4.
127. Thurl S, Munzert M, Henker J, et al. Variation of human milk oligosaccharides in relation to milk groups and lactational periods. Br J Nutr. 2010;104:1261–1271.
128. He Y, Liu S, Leone S, et al. Human colostrum oligosaccharides modulate major immunologic pathways of immature human intestine. Mucosal Immunol. 2014;7:1329–1339.
129. Newburg DS, Walker WA. Protection of the neonate by the innate immune system of developing gut and of human milk. Pediatr Res. 2007;61:2–8.
130. Fernández L, Langa S, Martín V, et al. The human milk microbiota: origin and potential roles in health and disease. Pharmacol Res. 2013;69:1–10.
131. Holscher HD, Davis SR, Tappenden KA. Human milk oligosaccharides influence maturation of human intestinal Caco-2Bbe and HT-29 cell lines. J Nutr. 2014;144:586–591.
132. Kainonen S, Rautava S, Isolauri E. Immunological programming by breast milk creates an anti-inflammatory cytokine milieu in breast-fed infants compared to formula-fed infants. Br J Nutr. 2013;109:1962–1970.
133. Singhal A, Lanigan J. Breastfeeding, early growth and later obesity. Obes Rev. 2007;8(suppl 1):S51–S54.
134. Karatas Z, Durmus Aydogdu S, Dinleyici EC, et al. Breastmilk ghrelin, leptin, and fat levels changing foremilk to hindmilk: is that important for self-control of feeding? Eur J Pediatr. 2011;170:1273–1280.
135. Socha P, Grote V, Gruszfeld D, et al. Milk protein intake, the metabolic-endocrine response, and growth in infancy: data from a randomized clinical trial. Am J Clin Nutr. 2011;94(suppl):1776S–1784S.
136. Escribano J, Luque V, Ferre N, et al. Effect of protein intake and weight gain velocity on body fat mass at 6 months of age: the EU Childhood Obesity Programme. Int J Obes (London). 2012;36:548–553.
137. 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–e1393.
138. DiSantis KI, Collins BN, Fisher JO, et al. 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. doi:10.1186/1479-5868-8-89.
139. Anderson SE, Gooze RA, Lemeshow S, et al. Quality of early maternal–child relationship and risk of adolescent obesity. Pediatrics. 2012;129:132–140.
140. DiSantis KI, Hodges EA, Fisher JO. The association of breastfeeding duration with later maternal feeding styles in infancy and toddlerhood: a cross-sectional analysis. Int J Behav Nutr Phys Act. 2013;10:53. doi:10.1186/1479-5868-8-89.
141. Steegers-Theunissen RPM. Quality of nutrition at conception, reproductive outcomes and long term health. In: Ama Nutri Cresci Nutrition Related Pregnancy Outcomes' Around the World. Milan, Italy: Fondazione Giorgio Pardi; 2015:28–29.
142. Koletzko B, Lien E, Agostoni C, et al. The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. J Perinat Med. 2008;36:5–14.
143. Ioannidis JPA. Evidence-based medicine has been hijacked: a report to David Sackett. J Clin Epidemiol. 2016;73:82–86.
144. Hill C, Guarner F, Reid G, et al. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014;11:506–514.
145. Ioannidis JPA. We need more randomized trials in nutrition – preferably large, long-term, and with negative results. Am J Clin Nutr. 2016;103:1385–1386.
146. Victora CG, Bahl R, Barros AJD, et al.; for Lancet Breastfeeding Series Group. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet. 2016;387:475–490.
147. Davanzo R, Romagnoli C, Costello G. Position Statement on Breastfeeding from the Italian Pediatric Societies. Ital J Pediatr. 2015;41:80. doi:10.1186/s13052-015-0191-x.
148. World Health Organization. Evidence for the ten steps to successful breastfeeding. http://www.who.int/nutrition/publications/evidence_ten_step_eng.pdf. Published (1998). Accessed February 26, (2016).