REVIEW

The Long-Term Effects of Dietary Nutrient Intakes during the First 2 Years of Life in Healthy Infants from Developed Countries: An Umbrella Review

Carlo Agostoni,[1] Anat Guz-Mark,[3] Luba Marderfeld,[3,4] Gregorio P Milani,[2] Marco Silano,[5] and Raanan Shamir[3]

[1] Pediatric Intermediate Care Unit, [2] Pediatric Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, DISCCO, Università degli Studi di Milano, Milan, Italy; [4] Institute of Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [5] Department of Clinical Nutrition and Dietetics, Schneider Children's Medical Center of Israel, Petah Tikva, Israel; and [6] Unit of Human Nutrition and Health, Department of Food Safety, Nutrition and Veterinary Public Health, Istituto Superiore di Sanità, Rome, Italy

ABSTRACT

The role of both qualitative and quantitative early nutrient intakes on later health has been suggested for decades and supported by observational studies on humans, mainly preterm and low-birth-weight infants, and animal models. However, to date, no comprehensive review has been conducted to evaluate the full impact of nutritional variables on healthy full-term infants. This umbrella review considers meta-analyses and systematic reviews on the health effects of different nutritional exposures or interventions in the first 2 y of life of healthy full-term infants in developed countries. The systematic reviews and meta-analyses published by March 2018 in MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews were included. The following outcomes were considered: growth and obesity, cardiovascular disease, neurodevelopment, allergy and autoimmunity, infections, and malignancy. Breastfeeding and complementary feeding were considered separately and analyzed by means of their differences in delivering heterogeneous food-related variables. The resulting data on the long-term effect of early nutritional differences in healthy full-term infants were found to be inconclusive. Only breastfeeding has a beneficial effect, which is nevertheless slight and limited to just a few outcome measures, whereas the type and duration required to be effective are still unclear. As regards the complementary feeding period, no clear effects of different dietary interventions emerge in terms of health outcomes. Available evidence on the health effects of differences in early nutrition in healthy full-term infants still remains largely inconclusive. *Adv Nutr* 2019;10:489–501.

Keywords: infants, children, later outcome of early nutrition, obesity, cardiovascular disease, neurodevelopment, allergy, autoimmunity, infections, malignancy

Introduction

The role of early nutrition and its impact on health and later outcomes have attracted increasing attention (1). In recent decades, the focus of pediatric nutrition studies has shifted from the consequences of unmet nutritional needs to the broader effect of specific nutrients on growth and adult health outcomes (2). This change has been driven by a large body of epidemiologic studies, most of which investigate the association between low birth weight and the development of disease in later life (3, 4). These data have led to the hypothesis that certain nutrients, in certain quantities and during certain critical sensitive periods, may have a long-term influence on endocrine, metabolic, and immune status (5), through various mechanisms including epigenetic changes of DNA expression (6). This theory is commonly termed "nutritional programming" (7).

On the whole, and in spite of the plethora of published reports, the real impact of either qualitative or quantitative differences in dietary intakes in the early years of life remains unclear, particularly in full-term infants. Several confounders (e.g., parental education and habits, ethnic background, and others) might indeed affect the strength or confute the validity of the available data (8, 9). It has also been suggested that the effects of early nutrition might be overestimated,

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Address correspondence to CA (e-mail: carlo.agostoni@unimi.it).
Abbreviations used: CD, celiac disease; ESPGHAN, the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; IQ, intelligence quotient; LC-PUFA, long-chain PUFA; RCT, randomized clinical trial; SES, socioeconomic status; T1D, type 1 diabetes.

at least in developed countries, as in developing countries tackling undernutrition remains the main goal (10, 11).

The purpose of this article is to review all the available meta-analyses and systematic reviews on the health and long-term effects of differences in early nutritional exposures or interventions in the first 2 y of life of full-term, healthy infants in developed countries. Accordingly, differences were related to the main health outcomes connected with development, quality of life, and the possibility of staying free of, or modulating, disease.

Methods

We conducted an umbrella review study, i.e., a systematic review of systematic reviews and meta-analyses. We applied the Joanna Briggs Institute methodology for umbrella reviews (12). For the details of the search, refer to the **Supplemental Methods**.

Results

Growth and obesity

After excluding duplications, 2817 potentially relevant citations were identified. Of these, 2634 articles were excluded by their title. The remaining 183 abstracts were assessed for eligibility. The full texts of 63 reviews were further screened and ultimately 39 publications fully met the inclusion criteria and were included in this part of the review (**Supplemental Figure 1**).

Breastfeeding.

Although the health benefits of breastfeeding are widely acknowledged, opinions and recommendations differ with regard to optimal duration. Eight systematic reviews (13–20) on this topic were identified and are detailed here. In 2004, Arenz et al. (13) were the first to publish a systematic review of the evidence concerning the protective effect of breastfeeding duration on childhood obesity. Nine studies with different breastfeeding durations, most of which divided feeding method by age 3 or 6 mo or by never or ever breastfed, were included. The authors concluded that breastfeeding seems to have a slight but consistent protective effect against obesity in children. In 2005, Owen et al. (14) published a systematic review that included 36 articles. Prolonged breastfeeding had a slightly higher protective effect on mean BMI than breastfeeding for a shorter period. In the meta-regression, each additional month of exclusive breastfeeding was associated with a decrease of 0.04 in mean BMI (in kg/m^2) (95% CI: 0.06, 0.01; $P = 0.008$). A closer investigation revealed that, within the meta-regression, the 3 studies that reported on exclusive breastfeeding for 8 mo showed a mean difference of 0.39 (95% CI: 0.26, 0.51); however, this protective effect was almost outweighed in 2 studies after adjustment for socioeconomic status (SES), maternal BMI, and maternal smoking. Overall, mean BMI was lower among breastfed subjects; however, this difference was small and potentially influenced by publication bias and inseparable confounding factors. The same year, Harder et al. (15) published a meta-analysis that showed an inverse relation with the risk of being overweight (regression coefficient: 0.94; 95% CI: 0.89, 0.98), with a dose–response relation that reached a plateau at a breastfeeding duration of 9 mo.

In a systematic review, Gale et al. (17) included 33 studies with 39 estimates on the effect of breastfeeding on the prevalence of overweightness and obesity. In a random-effects model, breastfed individuals were less likely to be considered overweight or obese, with a pooled OR of 0.78 (95% CI: 0.72, 0.84). Most of the reviewed studies compared breastfed subjects with those who were never breastfed. Other studies compared subjects who were breastfed for <2–3 mo, including those who were never breastfed, with those who were breastfed for longer periods. Few studies dealt with the duration of breastfeeding (either as a continuous or ordinal variable with several categories) in a way that allows dose–response analysis. Moreover, breastfeeding patterns (exclusive, predominant, or partial) were rarely assessed. The aforementioned review (17) investigated the association between breastfeeding or formula feeding and body composition in infancy. It included 15 studies that measured body composition using different techniques. In formula-fed infants, lean mass was greater at 3–4 mo [0.13 kg (0.03, 0.23 kg)], 8–9 mo [0.29 kg (0.09, 0.49 kg)], and 12 mo [0.30 kg (0.13, 0.48 kg)], and fat mass was lower at 3–4 mo [20.09 kg (20.18, 20.01 kg)] and 6 mo [20.18 kg (20.34, 20.01 kg)] than in breastfed infants. At 12 mo, fat mass was higher in formula-fed infants [0.29 kg (−0.03, 0.61 kg)] than in breastfed infants. In 2014, Yan et al. (18) published a systematic review on 25 studies. The results showed that breastfeeding is associated with a significantly lower risk of obesity in children (adjusted OR: 0.78; 95% CI: 0.74, 0.81). A categorical analysis of 17 studies revealed a dose–response relation between breastfeeding duration >7 mo and reduced risk of childhood obesity. No analysis was performed on breastfeeding duration cutoffs later than 7 mo.

Another systematic literature review was conducted by Lefebvre and John (19) in 2014. This review included 21 articles. Ten of the 21 studies concluded that breastfeeding had no significant effect on childhood obesity in children ≥4 y of age. The results of this review failed to show a clear relation between breastfeeding and protection from obesity.

One systematic review conducted in 2016 (20), including 23 studies with adjustment for SES, maternal BMI, and perinatal morbidity, showed a pooled reduction in the prevalence of overweightness or obesity of 13% (95% CI: 6%, 19%). The unclear effects, which are difficult to identify, of breastfeeding on later adiposity were investigated in the secondary analysis of a longitudinal randomized cluster trial in Belarus.

Based on the experimental design, only the effects of a nested controlled study, PROBIT, exploring the effect of breastfeeding intervention promotion on adiposity and blood pressure at age 16 y and on longitudinal growth trajectories from birth are available (21). PROBIT investigators assessed whether an intervention designed to promote exclusive and prolonged breastfeeding influenced children's

metabolic factors at the ages of 6.5 and 16.2 y. At the 16.2-y time point, 13,557 adolescents were examined out of a total of 17,046 healthy breastfed infants enrolled from 31 maternity hospitals and their affiliated clinics. Breastfeeding was never associated with a lower risk of later obesity, either at 6.5 y or at 16.2 y. On the contrary, the prevalence of overweight or obese subjects was significantly higher in the intervention arm. Because all mothers had initiated breastfeeding, these findings do not reflect a comparison of the effects of breastfeeding with those of formula feeding, but may be considered as adjusted for the initial intention to breastfeed or not and the related covariates. Given the inconsistent evidence available, the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) position paper (22) on breastfeeding concluded that the potential for breastfeeding to contribute to a reduction in later obesity still requires more detailed research.

Generally speaking, studies on breastfeeding and obesity can be affected by a variety of confounding variables—in particular, SES, maternal anthropometry, smoking, and loss to follow-up (23–27)—which are often not accounted for, or alternatively, are biased and poorly objective when they are assessed. The causative role of human milk as food or breastfeeding as behavior therefore still appears to be far from clear.

Complementary feeding.

Within the issue of growth and obesity, sufficient material allowed for subheadings including timing, macronutrient (protein, fat) contribution, and micronutrients, including pre- or probiotics.

Timing. In 2004, Morgan et al. (28) published a review using data from 5 UK cohorts to examine the impact of age at weaning on growth and health outcomes. Two of the cohorts involved full-term adequate-for-gestational-age infants. The authors found little evidence that weaning before or after 12 wk influences health outcomes ≤18 mo. Infants who were weaned early were larger at 12 wk than those weaned later, but by 18 mo no significant difference was observed. Moorcroft et al. (29) published a systematic review that included 24 articles. Most of the articles investigated the relation between introducing complementary feeding at 3, 4, and 6 mo and obesity or overweightness. This review did not find a clear association between the timing of the introduction of solid foods and obesity in infancy and childhood. Another systematic review (30) also showed introducing complementary foods between 4 and 6 mo to have no benefit. Vail et al. (31) evaluated whether an earlier weaning age (3–6 mo) promotes faster growth during infancy and besides conducting a primary analysis on a birth cohort study on 571 mothers of full-term singletons conducted in Cambridge, United Kingdom, they added a systematic review of 19 experimental and observational studies. The authors concluded that weaning between the ages of 3 and 6 mo has a neutral effect on infant growth in high-income countries. Because infants who gained weight faster between birth and 3 mo were weaned earlier than those with average or slower weight gain, the hypothesis of reverse causality could also be raised. A meta-analysis by Wang et al. (32), published in 2016, included 10 articles consisting of 13 studies that explored overweightness or obesity in children who started complementary feeding before or after 4 mo of age. The pooled results show that introducing complementary foods before 4 mo of age compared to at 4–6 mo was associated with an increased risk of being overweight (RR: 1.18; 95% CI: 1.06, 1.31) or obese (RR: 1.33; 95% CI: 1.07, 1.64) during childhood. Owing to insufficient dichotomous data, only 3 of the 5 studies on obesity and 6 out of 8 on overweightness were included in the analysis of children with a late introduction to complementary foods at ≥6 mo compared to 4–6 mo. The pooled RR of obesity was 1.02 (95% CI: 0.91, 1.14) and the RR of overweightness was 1.01 (95% CI: 0.90, 1.13), indicating a lack of a significant relation between delaying introduction of complementary foods to after 6 mo of age and being overweight or obese. Overall, there is insufficient evidence to suggest that early weaning or an early introduction of solids plays a role in the prevention of overweightness or obesity.

Protein. Three reviews have been published on the relation between protein and overweightness or obesity (33–35). Some of the studies included in these reviews observed a relation between high-protein formula and weight gain and body composition in young infants. All 3 reviews included the Child Obesity Project Trial (36). This trial is a multicenter randomized clinical trial (RCT) comparing weight and height at ages 3, 6, 12, 24 mo, and 6 y for low- and high-protein content formulas. Formula-fed infants were switched to a purpose-made low-protein formula (1.77 and 2.2 g protein per 100 kcal in infant and follow-on formula, respectively) or a high-protein formula (2.9 and 4.4 g protein per 100 kcal, respectively), which used the minimum and maximum limits permitted by the European regulations for both types of formula at the time of project planning. The casein/whey ratio was the same as in cow milk for both types of formula used. The difference in BMI *z* score was 0.2 at age 6 y and was mostly accounted for by the BMI percentile curves ≥90th percentile for the groups. Although this finding was statistically significant, its clinical relevance may be debatable because the weight difference in grams was narrow ($P = 0.009$). There were also a number of methodological issues limiting the generalization of the findings. For instance, *1*) recruitment involved infants with an age of ≤8 wk, and the median age at recruitment was ∼2 wk (IQR: 3–30 d), thus also including infants who were initially breastfed; *2*) the high protein content of the 2 high-protein formulas (infant and follow-on) and quality are unrealistic today and certainly out of line with the forthcoming 2019 European regulations for milk-based products; *3*) the fat content of the high-protein formula, which was modified in order to achieve the same energy intake across the 2 formulas, is relatively lower, making it impossible to consider protein content as the only variant [the possible role of the early fat/protein balance on later

adiposity was described in detail by Rolland-Cachera et al. (37)]; and *4*) the differences at 6 y are restricted to the highest BMI percentiles.

Fats. We identified 6 reviews (38–43) on the relation between PUFA intake and infant growth published since 2001. Some of these reviews included also neurodevelopmental and visual acuity outcomes. Three of the reviews, including a Cochrane review published in 2017, performed meta-analyses (39, 40, 43). The results of the meta-analyses were consistent with reviews conducted previously that showed no significant differences between the intervention and control groups with respect to weight, length, and head circumference either at <1 y of age or in later childhood.

Other micronutrients and additives. Systematic reviews on fortification of food or supplements with micronutrients such as zinc, folate, and iron were identified in the literature. However, all of these reviews included trials conducted in developing countries and included different subjects—ill and healthy, mature and premature. No separate analyses were performed for high-income countries and healthy infants in these studies. No conclusions can be drawn regarding early supplementation and later outcomes on the basis of these reviews (44–51). Prebiotics and probiotics are increasingly added to infant formula. Five systematic reviews (52–56), including the ESPGHAN position paper (53), have been performed in recent years, in order to summarize current knowledge on the related effects on growth. Most trials had short follow-up periods and included a small number of patients. None of the articles found that a dietary intake of these compounds benefits growth in well-nourished children in developed countries. The ESPGHAN position paper concluded that few probiotic strains used to supplement infant formula support normal growth in healthy full-term infants (53).

In conclusion, the causality of the relation between breastfeeding, particularly if prolonged, and some macro- and micronutrients and a reduction of obesity risk in later life remains almost speculative, owing to a lack of appropriate clinical studies and some unavoidable bias in evaluating confounding variables, at least in high-income countries. However, these observations do not represent grounds for a change in the WHO recommendations on breastfeeding, which remains the optimal way to feed infants up to the age of 6 mo, regardless of specific health outcomes.

Neurodevelopment

After excluding duplications, 1210 potentially relevant citations were identified. Of these, 1136 articles were excluded because their titles were incompatible with the search criteria. The remaining 74 abstracts and full-text articles were assessed for eligibility and ultimately 15 publications were included (**Supplemental Figure 2**). Unlike the previous sections, a subheading is added under breastfeeding, relating to infants' dietary enrichment with long-chain PUFAs (LC-PUFAs). This subheading is consistent with the mass of studies arising from the observations that the direct supply of preformed LC-PUFAs with human milk might support the biological plausibility of sustained anatomic and functional neurodevelopment support. For the sake of consistency, LC-PUFA dietary enrichment in bottle-fed infants is also included under the same subheading.

Breastfeeding.

The relation between breastfeeding and intellectual performance was first reported in 1929 (57), and the first meta-analysis was published in 1999 (58). In this review, Anderson et al. (58) performed a meta-analysis of 11 eligible studies, which reported covariate-adjusted findings comparing the cognitive development of breastfed and formula-fed subjects during childhood and adolescence. After adjustment for covariates, the authors found a significant increment in cognitive function of 3.16 (95% CI: 2.35, 3.98) intelligence quotient (IQ) points in breastfed compared with formula-fed children. The difference before adjustment for confounding covariates was much higher: 5.32 (95% CI: 4.51, 6.14) points, demonstrating the strong potential effect of cofactors such as SES and maternal education and IQ. The authors examined the stability of the effect of breastfeeding separately across different age classes (6–23 mo, 2–5 y, 6–9 y, and 10–15 y at cognitive function evaluation). In their meta-analysis, there was no evidence for an age-associated trend, and the results suggested that a significant developmental augmentation attributable to breastfeeding is established early in life and persists at least through to mid-adolescence. In 2000, Drane and Logemann (59) set 3 criteria for evaluating the validity of studies regarding breastfeeding and cognitive development: clearly defined outcome, specification of partial and exclusive breastfeeding, and control of confounding variables. Of the 6 studies on full-term infants meeting these standards, 4 studies found an advantage for breastfeeding compared with formula-feeding of 2–5 IQ points. Two studies meeting these standards did not find statistically significant associations between the type of feeding and IQ, although the authors highlighted the fact that, in these studies, IQ was evaluated at a young age or after a relatively short duration of breastfeeding. The authors of this systematic review concluded that the association between infant feeding and cognitive development has a long and detectable effect between 5 and 18 y of age. Jain et al. (60) were even stricter in their eligibility criteria, evaluating 8 methodological aspects, including study design, sample size, target population, quality of feeding data, control of susceptibility bias, blinding, outcome measures, and format of results. The authors stated that of the 40 studies reviewed, 68% reported that breastfeeding has a beneficial effect on intelligence, but only 2 studies met their methodological quality standards. Of these 2 studies, 1 (61) concluded that the effect of breastfeeding on intellect was significant, and the other did not (62). Der at al. (63) performed a meta-analysis controlling specifically for maternal intelligence (as opposed to maternal education and SES alone). Before adjustment, breastfeeding was associated with an increase in mental

ability of ∼4 points; however, the adjustment for maternal intelligence accounted for most of this effect. After fully adjusting for the relevant confounders including mothers' intelligence, the investigators did not find breastfeeding to have any significant effect on children's cognitive performance (0.52 points; 95% CI: 0.19, 1.23 points). According to this review, the role of environmental confounders was the main culprit for the described differences in favor of breastfed full-term infants. Following on from the results from this meta-analysis, Walfisch et al. (64) stated in their 2013 review that, unlike earlier studies, the studies from the last decade in general tried to control for family SES and parental education and intelligence. Of the >80 studies evaluated in their review, 33% showed a positive relation between breastfeeding and IQ, 47% showed no relation, even initially or only after adjustment for confounders, and 20% showed a diminished but still statistically significant relation after adjustment. They concluded that much of the reported effect of breastfeeding on pediatric neurodevelopment is due to the major demographic confounders and is unlikely to be due to breast milk as food itself.

Despite the great heterogeneity of the different studies, Horta et al. (65) conducted a large systematic review and meta-analysis on the relation between breastfeeding and performance in intelligence tests, only including studies that adjusted results also for stimulation or interaction at home. This analysis showed that breastfed subjects achieved a higher performance in intelligence tests with a mean difference of 3.44 points (95% CI: 2.30, 4.58 points). Studies that controlled for maternal IQ showed a smaller, but still significant, benefit for breastfeeding of 2.62 points (95% CI: 1.25, 3.98 points). The pooled benefit of breastfeeding in studies that evaluated subjects aged between 10 and 19 y was smaller than in studies involving younger subjects (1.92 points compared to 4.12 points of IQ, respectively). Overall, the authors concluded that breastfeeding probably has a beneficial causal effect on cognitive development, even beyond the contributing cofactors such as maternal IQ and environmental confounders.

No systematic reviews or meta-analyses on breastfeeding duration and its effect on IQ were identified. Whereas 1 large study published in 2002 (66) comparing breastfeeding durations of <1 mo, 2–3 mo, 4–6 mo, 7–9 mo, and >9 mo suggested a positive correlation between the breastfeeding duration and IQ scores in early adulthood, other studies were less specific, therefore precluding the possibility of performing an accurate meta-analysis on the duration of breastfeeding and its relation with neurodevelopment.

LC-PUFA supplementation. The presumed positive effect of breastfeeding on infants' brain development has been attributed (among other factors) to the presence of DHA in human milk. The strength of this biological plausibility derives mainly from observations of clear differences in fat composition at autopsy of the brains of infants after sudden infant death syndrome (67, 68); it was further confirmed by studies with tracers in animals (69).

This led certain manufacturers to supplement infant formulas with either omega-6 (arachidonic acid, ARA) or ω-3 (EPA, but especially DHA) LC-PUFAs, in an attempt to mimic the functional qualities of human milk, as well as the mere biochemical effects. Many studies, including several RCTs, have attempted to evaluate the effect of such supplementation on the development of full-term infants, with conflicting results. A large body of studies included preterm infants, who are theoretically exposed to more evident effects of dietary LC-PUFA enrichment, and did not, therefore, meet our inclusion criteria. In 1 comprehensive systematic review, Campoy et al. (41) assessed the evidence of the short- and long-term effects of n–3 LC-PUFA supplementation on the visual acuity, psychomotor development, and mental performance of children. Most of the RCTs reviewed in this publication failed to demonstrate any clear benefit of LC-PUFA supplementation on cognitive performance. Although some studies reported favorable results in one specific area of infantile development over another, especially the development of visual acuity, no sustained uniform effect was clearly identified. There was also great heterogeneity among studies regarding the timing, type, concentration, and duration of LC-PUFA supplementation.

We identified 2 large meta-analyses published over the last decade that addressed the effect of LC-PUFA supplementation on the neurodevelopment of full-term infants, using different methodologies (70–72). All 2 meta-analyses came to similar conclusions: that the supplementation of infant formula with LC-PUFAs has no proven clinical effect on psychomotor or mental developmental and cognitive assessments of healthy full-term infants and children. One Cochrane review mentioned previously (43) analyzed 11 studies assessing neurodevelopmental outcomes at or before 2 y of age. Only 2 of these studies reported beneficial effects, and the vast majority failed to support any significant effect. Moreover, the follow-up of some infants in different studies at 3, 6, and 9 y of age revealed that supplementation has no beneficial effect. The authors concluded that routinary supplementation of full-term infant milk formula with LC-PUFAs cannot be recommended at this time.

Complementary feeding.

The role of complementary feeding in neurodevelopment is unclear, and there are no systematic reviews or meta-analyses available on this topic for specific macronutrients or foods. More studies consider the role of micronutrients, but the possible effects may be shown in developmental settings, which does not meet our inclusion criteria. The most recent position paper by ESPGHAN on complementary feeding (73) involved a systematic literature search regarding the different aspects of complementary feeding in relation to current data on various outcomes. The ESPGHAN position paper discussed meat and LC-PUFAs and their relation with cognitive development, and concluded that the results available are inconsistent or conflicting owing to heterogeneous study designs based on small sample sizes. The ESPGHAN

Committee on Nutrition concluded that the current data are insufficient for making specific recommendations for choices or the composition of complementary feeding based on cognitive outcome.

Micronutrients.

In spite of there being a plethora of publications regarding micronutrient deficiencies (mainly iron, folic acid, zinc, and iodine) among infants in developing countries, data regarding the effect of micronutrient supplementations in healthy infants from developed countries are more limited and focus mainly on zinc and iron. A systematic review and meta-analysis regarding zinc supplementation and pediatric mental and motor development was published in 2014 (74). Five RCTs were included in the analysis and assessed the Mental Development Index and Psychomotor Development Index mainly using the Bayley Scales of Infant Development at different ages. When the pooled results were summarized, no association was found between zinc intake during infancy, and mental and motor development in infants and young children. In a recent up-to-date systematic review (75), 5 RCTs addressing iron supplementation during infancy (0–9 mo) and developmental evaluation up to the age of 3 y were identified. None of these RCTs individually showed any beneficial effect of iron supplementation during early life on Mental Development Index scores during the first 18 mo. Three studies showed that iron supplementation had a beneficial effect on Psychomotor Development Index scores at some time points, whereas 2 did not. One follow-up study evaluating the influence of early supplementation on cognitive performance and school performance at the age of 9 y (76) was identified. No statistically significant difference between the study groups was found. Accordingly, the limited existing evidence may suggest that iron supplementation has a positive effect on infantile psychomotor development, but not on cognitive development or behavior. Overall, the evidence from current data is still conflicting and weakened by possible effects only in subgroups of infants effectively suffering from limited availability of iron at the time of recruitment.

The issue of multiple micronutrient intake is restricted to data from developing countries and therefore outside the declared scope of this umbrella review.

In conclusion, current literature on the long-term effect of early-life nutritional manipulations on pediatric neurodevelopment is still conflicting. The most widely studied aspect in this field is breastfeeding during the first few months of life, with durations varying between a few weeks and 6 mo. This research suggests that breastfeeding has some beneficial effects on intelligence and cognitive performance, but it is almost impossible to fully control for confounders and hidden bias. Currently, no other nutritional interventions during the first 3 y of life have been proven to have any sustained effect on pediatric neurodevelopment in healthy full-term infants in high-income countries.

Allergy and autoimmunity

After excluding duplications, 1687 potentially relevant citations were identified. Of these, 1535 articles were excluded because their titles were incompatible with the desired search definition and 110 were excluded because they were abstracts. Full-text articles were assessed for eligibility and ultimately 8 publications included in this part of the review were found to meet the inclusion criteria (**Supplemental Figure 3**). Within this area, the procedure of subdividing into breastfeeding and complementary feeding sections requires an additional subdivision among the main clinical areas of interest with regard to outcomes, which are represented by celiac disease (CD), IgE-mediated food allergy, and type 1 diabetes (T1D) with related autoimmune disorders.

CD.

Breastfeeding. The ambitious goal that CD might be prevented by the practice and the duration of breastfeeding has long been supported by the early epidemiological studies in the field. In 2006, a meta-analysis by Akobeng et al. (77) reported a significant OR of 0.5 in favor of breast milk over formula. However, several subsequent studies did not confirm this effect and a recent meta-analysis (78), including the seminal prospective studies CELIPREV and PREVENTCD both published in 2014 (79, 80), concluded that a nonsignificant preventive effect was observed for both breastfeeding itself and for its duration on the development of CD in genetically predisposed infants. Likewise, the type of formula (cow milk protein or extensively hydrolyzed formulas) used to feed infants of $\leq$8 mo of age did not affect the risk of developing CD (81).

Complementary feeding. The timing of the first introduction of gluten during weaning is another infant feeding practice whose modulation was thought to have an impact on the onset of CD in "at-risk" children. One systematic review concluded that the infant's age at their first exposure to gluten has no effect on the clinical development of CD (82). Early (at 4 mo of age) and late (at 12 mo of age) introduction of gluten have been seen to result in the same prevalence of CD at 8 y. The only difference observed between the 2 groups was that in those infants who were exposed to gluten for the first time within the first year of life, the clinical onset of CD occurred at a mean age of 5 y, compared with a mean age of 8 y in those who received gluten for the first time after the age of 1 y. It remains to be elucidated whether the later development of overt CD offers an advantage for the affected children, for instance by protecting their neurological and psychological development.

The question of whether the amount of gluten given during the weaning period might play a pivotal role in triggering the onset of CD is still unanswered. The most recent meta-analysis included just 1 retrospective observation (83) and was unable to draw a consistent conclusion from intervention trial data.

IgE-mediated food allergy.

Breastfeeding. No high-quality studies were found relating to the risk of food allergy among breastfed infants compared with bottle-fed infants. Once more, the ethical impossibility of randomly assigning children to breastfeeding or formula feeding must be emphasized. However, based on prospective observation cohorts, 1 Cochrane systematic review (84) concluded that there is no evidence to support short-term or prolonged feeding with hydrolyzed formula compared with exclusive breastfeeding for the prevention of allergy. It also concluded that the only evidence suggesting that short-term use of a hydrolyzed milk formula is effective in preventing cow milk protein allergy compared to a standard cow milk formula is of a poor quality. Even the WHO recommendation to introduce allergenic foods while the infant is still being breastfed is, at the current state of knowledge, supported by the putative biological effect of the immune-competent molecules of the breast milk rather than by epidemiological evidence (85).

Complementary feeding. One recent meta-analysis, which screened >16,000 articles regarding the effects on allergy risk of modulating the timing of food introduction, found that an early (from 4–6 mo of age) introduction of allergenic food lowered to 0.56 (95% CI: 0.36, 0.87) the risk of developing egg allergy and to 0.29 (95% CI: 0.11, 0.74) the risk of peanut allergy, compared with a late introduction (from 7 mo of age) (86). The timing of first introduction of cow milk was not seen to have any effect. The studies included in the meta-analysis are characterized by significant limitations, consisting in the heterogeneity of the populations studied, the different interventions spanning from a single food to a multidisciplinary approach considering also environmental pollution and tobacco smoke exposure, and, finally, the varying length of the follow-up period. Consequently, these results ought to be translated into daily practice with caution. As a matter of fact, 1 very recent RCT conducted in Singapore on 1152 infants did not find an increased prevalence of egg, peanut, and shellfish allergy at 4 y of age, when these foods were introduced after 10 mo of age (87). In our opinion, the confirmation of these last unexpected observations regarding the timing of solid food introduction and allergy development justifies a supplementary description of this single trial.

T1D and autoimmune disorders.

One meta-analysis found that exclusive breastfeeding for >2 wk has a very weak protective effect on the risk of T1D (88). The limited data available from observational studies and RCTs suggest that gluten introduction (89) and the quality and type of cow milk proteins administered in the first year of age (standard or extensively hydrolyzed formula) (90, 91) have no effect on the later risk of T1D.

Infections

After excluding duplications, 5027 potentially relevant citations were identified. Of these, 4845 articles were excluded because their titles were incompatible with the desired search definition and 133 were excluded because they were abstracts. Full-text articles were assessed for eligibility and ultimately 21 publications fulfilling the inclusion criteria were included in this part of the review (**Supplemental Figure 4**). Consistent with the approach adopted previously, the procedure of subdividing breastfeeding and complementary feeding required a preliminary subdivision among the main clinical areas of interest, represented by acute otitis media, and infections of the lower respiratory tract and gastrointestinal tract. Interventions in the complementary feeding period did not examine specific solids or macronutrients but focused on single micronutrients, mostly those with pre- and probiotic effects. As regards outcomes, the "Infections" area mainly concerned immediate, or short-term, health effects, whereas the other 5 areas analyzed mainly regarded medium- and long-term outcomes.

Acute otitis media.

Breastfeeding. The first meta-analysis on the relation between breastfeeding and acute otitis media was conducted by Uhari et al. (92) in 1996. This report included 10 studies (2 case control and 8 cohort studies) showing that breastfeeding infants for ≥3 mo resulted in a reduced risk of acute otitis media (RR: 0.87; 95% CI: 0.79, 0.95). However, this first meta-analysis did not report data on the heterogeneity and potential confounding factors (e.g., parental smoking or attendance of day care) of the included studies. A more thorough systematic review on breastfeeding and acute otitis media in exclusively breastfed compared with exclusively formula-fed healthy infants was performed by the US Agency for Healthcare Research and Quality (93) in 2007. In their search strategy, all definitions of "exclusively breastfeeding" as provided by the different studies were accepted. The authors conducted their analysis on 10 studies (2 case control and 8 cohort studies). Seven out of the 10 studies included were published after Uhari et al.'s meta-analysis. Six studies were used for the meta-analysis (2 studies comparing "ever and never" and 4 studies comparing 3- and 6-mo exclusive breastfeeding categories). In this meta-analysis, all included studies had good and moderate methodological quality and the cumulative results were adjusted for potential confounders. The overall pooled OR for developing acute otitis media was 0.77 (95% CI: 0.64, 0.91) for exclusively breastfed infants. In the latter group, breastfeeding for ≥3 mo had a significant protective effect on acute otitis media (RR: 0.87; 95% CI: 0.79, 0.95) but not on its recurrence (RR: 0.69; 95% CI: 0.46, 1.03). Similarly, breastfeeding for ≥6 mo had a stronger protective effect than breastfeeding for <6 mo (RR: 0.69; 95% CI: 0.49, 0.97). In 2009, a systematic review by Duijts et al. (94) identified 4 prospective studies correlating breastfeeding with the frequency or recurrence of acute otitis media. One study found that breastfeeding has a protective effect on acute otitis media in exclusively breastfed infants compared with nonbreastfed ones; another study observed a protective effect of 4–6 mo of breastfeeding compared with <4 mo, and another one a protective effect of breastfeeding

for ≥6 mo as opposed to <6 mo. In 2010, a systematic review by McNiel et al. (95) once again addressed the role of exclusive breastfeeding. The authors only included studies in which the definition of fully breastfeeding excluded any formula use. They included 4 cohort studies, all of which found a significant correlation between formula use and an increased occurrence of acute otitis media. This meta-analysis found a pooled OR of 2.00 (95% CI: 1.40, 2.78) for acute otitis media if exclusive breastfeeding was interrupted between 3 and 6 mo. The results were not adjusted for confounders. In 2012, a Cochrane review performed by Kramer and Kakuma (30) investigated the effect of the duration of breastfeeding on the occurrence of acute otitis media. Two observational studies were included. The pooled data of these studies identified a slightly higher risk of ≥1 episode of acute otitis media during the first year of life (RR: 0.81; 95% CI: 0.43, 1.52) for 3 compared with 7 mo of exclusive breastfeeding. In 2015, Bowatte et al. (96) performed a further systematic review and meta-analysis. This study included children with high risk of allergy, but without known comorbidities. The authors selected 24 articles (18 cohort and 6 cross-sectional studies) and found that breastfeeding has a significant protective effect for acute otitis media limited to the first 2 y of life in the following categories: "ever" compared with "never" breastfeeding (OR: 0.67; 95% CI: 0.56, 0.80), "more" compared with "less" breastfeeding (OR: 0.67; 95% CI: 0.59, 0.76), and, finally, "exclusive" compared with "nonexclusive" breastfeeding for the first 6 mo (OR: 0.57; 95% CI: 0.44, 0.75). Finally, the 2016 review by Victora et al. (20) confirmed the protective effect of breastfeeding on acute otitis media up to the age of 2 y.

Complementary feeding. The number of studies investigating the role of complementary feeding and dietary components in the prevention of acute otitis media is very limited. Elemraid et al. (97) performed a systematic review in 2009 and identified 1 study addressing the role of iron supplementation. Infants receiving iron-fortified infant formula did not present a significant difference for the development of otitis media compared with infants fed cow milk–based infant formula. In 2006, ESPGHAN performed a systematic review including only randomized controlled trials on formula supplementation. This systematic review found that infants fed a formula supplemented with galacto-oligosaccharides or fructo-oligosaccharides had a similar risk of acute otitis media to those fed formula without supplements (RR: 0.7; 95% CI: 0.2, 2.2) (49). Similarly, Lohner et al. (51) performed a systematic review on the use of prebiotics in infant formula and identified only 1 trial, which found that prebiotics have no effect on the risk of acute otitis media. In 2013, Liu et al. (98) included 4 RCTs investigating the role of *Lactobacillus rhamnosus* GG in the reduction of episodes of acute otitis media in a systematic review. The authors found that the supplemented probiotic species (RR: 0.76; 95% CI: 0.64, 0.91) have a significant protective effect, despite the fact that for 2 of the 4 RCTs intervention was limited to the early phases of life. In 2012, Ochoa et al. (99) performed a systematic review on the role of lactoferrin-supplemented formula, identifying only 1 trial, which did not find any difference between fortified formula– and formula-fed infants for the risk of developing acute otitis media. Accordingly, most systematic reviews dealing with this issue are limited to just 1 RCT, thus lowering the strength of the final conclusions.

Lower respiratory tract infections.

Breastfeeding. In 2003, Bachrach et al. (100) performed a meta-analysis and pooled the results of 7 cohort studies comparing the risk of hospitalization for lower respiratory tract infections in exclusively breastfed and nonbreastfed infants. Exclusive breastfeeding was defined as little or no formula offered. The authors initially identified 33 studies, all of which found breastfeeding to have a protective effect. However, only 7 studies were pooled for the meta-analysis. The latter suggested that formula feeding was associated with a 3.6-fold higher risk of hospitalization than ≥4 mo exclusive breastfeeding. In 2004, Kramer and Kakuma (101) performed a systematic review investigating the role of exclusive breastfeeding compared with mixed feeding for between 3 and 7 mo. They excluded studies with infants breastfed <3 mo. This report identified 2 studies, which did not disclose any significant advantage from longer breastfeeding with regard to the prevention of lower respiratory tract infections. The US Agency for Healthcare Research and Quality (102) performed a search of available meta-analyses in 2007. In this report, just 1 meta-analysis was identified (the aforementioned meta-analysis by Bachrach et al.) and was rated as being of a good quality. In 2009, a systematic review performed by Duijts et al. (94) identified 6 prospective studies correlating breastfeeding with lower respiratory tract infections. Five out of 6 studies reported a decreased risk of lower respiratory tract infection during the first 24 mo of life in breastfed infants. One study did not find any relation between exclusive breastfeeding for 3 mo and risk of ≥2 respiratory infections up to the age of 1 y. In 2010, McNiel et al. (95) pooled 5 prospective studies considering the role of exclusive breastfeeding (included expressed human milk) compared with any formula use. In just 1 of these 5 studies, a significant protective role was observed for breastfeeding, and this was limited to the risk of hospitalization for lower respiratory tract infections. In a Cochrane review by Kramer and Kakuma in 2012 (30), 2 trials investigating the association between breastfeeding and lower respiratory tract infections were identified. The pooled crude results of the 2 trials showed a significant reduction in the risk of hospitalization for respiratory tract infection (pooled RR: 0.75; 95% CI: 0.60, 0.94) in infants exclusively breastfed compared with mixed-fed for 3–7 mo. However, in a multivariate analysis including geographic region, urban or rural location, maternal education and cigarette smoking, and number of siblings in the household, the difference was not statistically significant (adjusted OR: 0.96; 95% CI: 0.71, 1.30). In 2015, Shi et al. (102) performed a systematic review on studies focusing on risk factors for

respiratory syncytial virus in children <5 y. The authors identified just 1 study investigating the role of breastfeeding, which was not found to be significantly associated with respiratory syncytial virus in the multivariate analysis.

Complementary feeding. In 2011, Braegger et al. (53) performed a systematic review investigating the role of probiotic supplementations in preventing lower respiratory tract infections. In their analysis, very limited data suggested that probiotics are not associated with a lower number of respiratory tract infections. Similar conclusions were drawn in more recent systematic reviews performed by Liu et al. (98) in 2013, Lohner et al. (51) in 2012, and Skórka et al. (103) in 2017. Ochoa et al. (99) performed a systematic review on the role of lactoferrin-supplemented formula in 2012. In this systematic review, 1 RCT reported a protective effect on lower respiratory tract illnesses after 12 mo supplementation (0.15 episodes/y) compared with regular formula (0.5 episodes/y). In 2017, Jat (104) performed a systematic review (and meta-analysis) and identified 1 study investigating the relation between vitamin D concentrations in cord blood and the risk of respiratory syncytial virus infection in infants. In this study, the concentrations of vitamin D in cord blood were lower in patients with respiratory syncytial virus infections than in infants without infections (65.7 compared with 84.1 nmol/L, $P = 0.009$) in the first year of life. From a more practical standpoint, an ESPGHAN position paper published in 2017 suggested that the introduction of solids alongside breastfeeding does not result in a change in the risk of developing lower respiratory tract infections (73).

Gastrointestinal infections.

Breastfeeding. In a review performed in 2004 by Kramer and Kakuma ((101), just 1 study comparing exclusive and mixed breastfeeding was selected. In this study, exclusively breastfed infants had a lower risk of having ≥1 episode of gastrointestinal infection in the first 12 mo of life (RR: 0.67; 95% CI: 0.46, 0.97), even after adjustment for confounders. At the same time, there was no difference in the risk of hospitalization for gastrointestinal infections. A systematic review by Duijts et al. (94) published in 2009 identified 8 studies on breastfeeding and gastrointestinal infections. Six of these suggested that breastfeeding has some beneficial effects for the prevention of gastroenteritis. However, the protective effect varied greatly between the studies according to the duration and exclusivity or not of breastfeeding. In 2016, Krawczyk et al. (105) performed a systematic review on the association between breastfeeding and rotavirus infections. The authors identified 1 cohort study reporting a similar rate of infections between breastfed and bottle-fed infants, although milder forms were observed in the former group. Finally, the role of breastfeeding in the prevention of *Helicobacter pylori* infection was investigated in 2009 by Chak et al. (106). The authors identified 7 studies dealing with this issue. All but 1 study did not find a significant relation between breastfeeding and lower rates of *Helicobacter pylori* infection. The pooled data of the 7 studies confirmed a nonsignificant association. Similar conclusions were reported in another systematic review conducted by Carreira et al. (107) in 2015.

Complementary feeding. After conducting a systematic review in 2011, ESPGHAN stated that limited evidence suggests that supplementation of infant formula with probiotics does not reduce the risk of nonspecific gastrointestinal infections in children (53). In 2014, Lohner et al. (108) performed a systematic review on prebiotics and infections. The authors identified just 1 randomized controlled trial that did not detect any statistical difference between infants fed formula with or without long-chain galacto-oligosaccharide or fructo-oligosaccharide supplementation. Finally, the aforementioned ESPGHAN position paper of 2017 suggested that, as for lower respiratory tract infections, the introduction of solids alongside breastfeeding does not result in an increase in the risk of gastrointestinal infections (73).

To conclude, epidemiologic evidence is now overwhelming that breastfeeding protects against acute otitis media and lower respiratory tract and gastrointestinal infections in low- and middle-income countries; however, the data are scarce for high socioeconomic countries. Breastfeeding would appear to have a beneficial effect on mild infections and most data suggest a protective duration/amount–response effect. Biological plausibility may be offered by the multiplicity of immune-active factors (such as secretory IgA antibodies, lactoferrin, and immuno-stimulating cytokines) contained in human milk (109). The role of breastfeeding is not univocally supported in more severe infections (e.g., infections requiring hospitalizations). This discrepancy could be due to the methodological flaws of published studies: in particular, the failure to control for all confounding variables. Furthermore, most available studies differ with regard to the definition of the diagnostic criteria, the length of follow-up, and, above all, the definition of the type of breastfeeding. Finally, some studies could not be compared because they did not make a clear distinction between the diagnosis of acute otitis media and upper and lower respiratory tract infections. As for the other dietary interventions, the available data are very limited and mostly too inconclusive to reach any evidence-based conclusion.

For the results regarding the effect of early nutrition on cardiovascular diseases and malignancies, see **Supplemental Results 1** and **2** and **Supplemental Figures 5** and **6**.

Strengths and Limitations

This umbrella review allowed for a very extensive and thorough examination of an enormous amount of data enriching the literature over many years of research. The main methodological limitation is the inclusion of data from systematic reviews and meta-analyses alone, which may exclude some isolated specific studies if they were not retrieved and reviewed in the past and may also exclude studies showing effects that were not pooled in a systematic review or a meta-analysis. Several studies applied different

inclusion criteria for the selection of the primary studies (with varying definitions of breastfeeding, in particular). Furthermore, the different search methods and limitations used might account for further heterogeneity in the included systematic reviews and meta-analyses. These factors might affect the comparability of the studies considered. On the other hand, we attempted to restrict our analysis to a homogeneous group of subjects, i.e., full-term healthy infants in high-income countries. This specific study population may have different characteristics to preterm infants, as well as infants suffering from malnutrition in developing countries, and our conclusions cannot be extended to these populations. The results of available systematic reviews and meta-analyses are, in some cases, partially overlapping because of the restricted number of large studies potentially available for inclusion. Finally, the quality of the systematic reviews and meta-analyses included in this umbrella review in no case completely fulfilled the 16 items of the AMSTAR 2 grading system (110) (**Supplemental Tables 1** and **2**).

Conclusions

In healthy infants from developed countries, with no prior history of prematurity or malnutrition, the current evidence on either medium- or long-term effects of differences in early nutrition habits or interventions is quite limited. The beneficial effects of breastfeeding are limited to just a few outcomes, whereas the type (e.g., exclusive compared with partial) and duration of breastfeeding are not well defined in many studies and, therefore, not comparable. As a consequence, most revisions should a posteriori apply heterogeneous definitions of breastfeeding and formula feeding (exclusive, partial, ever compared with never). In some instances, the effects of breastfeeding have a short duration or little clinical impact—for example, a slightly protective effect limited to mild infections of the respiratory and gastrointestinal tracts, as well as a minimal neurocognitive advantage after at least partial adjustment for confounders; however, these effects could be affected by a number of potential biases. All of these findings, however, are limited to healthy infants in high-income countries. Nutritional intervention could have more evident and measurable effects in malnourished children and in premature infants, but these populations are outside the scope of this umbrella review. Finally, as far as the complementary feeding period is concerned, no clear effects of different dietary interventions emerge at long-term follow-up.

In short, to date, according to this large-scale comprehensive review, the evidence available on the long-term effects of differences in early nutrition in healthy full-term infants from developed countries is mostly inconclusive.

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