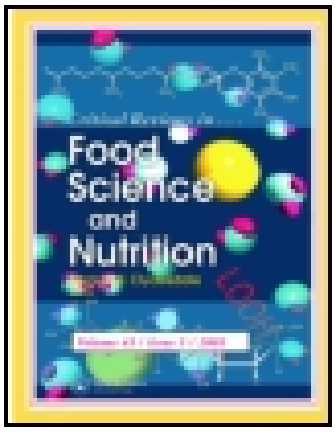

Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

Nutrition of Infants and Young Children (1-3 Years) and its Effect on Later Health: A Systematic Review of Current Recommendations (EarlyNutrition Project)

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Accepted author version posted online: 09 Mar 2015.

To cite this article: Bartłomiej Mateusz Zalewski, Bernadeta Patro, Margriet Veldhorst, Stefanie Kouwenhoven, Paula Crespo Escobar, Joaquim Calvo Lerma, Berthold Koletzko, Johannes Bernard Van Goudoever & Hania Szajewska (2015): Nutrition of Infants and Young Children (1-3 Years) and its Effect on Later Health: A Systematic Review of Current Recommendations (EarlyNutrition Project), Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2014.888701

To link to this article: http://dx.doi.org/10.1080/10408398.2014.888701

NUTRITION OF INFANTS AND YOUNG CHILDREN (1-3 YEARS) AND ITS EFFECT ON LATER HEALTH: A SYSTEMATIC REVIEW OF CURRENT RECOMMENDATIONS (EarlyNutrition Project)

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ABSTRACT

Background. EarlyNutrition (www.project-earlynutrition.eu) is an international research project investigating the effects of early nutrition on metabolic programming.

Objective. To summarize, by performing a systematic review, current standards, recommendations, guidelines, and regulations (hereafter, referred to as documents) on the nutrition of children up to 3 years of age. Special emphasis was placed on long-term effects of early nutrition, such as the risk of cardiovascular disease, hypertension, overweight, obesity, metabolic syndrome, diabetes, or glucose intolerance.

Methods. MEDLINE, selected databases, and websites were searched for documents published between 2008 and January 2013.

Results. Forty-two documents met the inclusion criteria. The strongest and most consistent evidence for a protective, long-term effect was documented for breastfeeding. Also, limiting the intake of sodium and rapidly absorbed carbohydrates, use of a specific meal pattern, reducing the consumption of saturated fatty acids by replacing them with polyunsaturated fatty acids, and lowering the intake of trans fatty acids, seems beneficial. Many documents did not evaluate long-term outcomes of interest to us, or reported insufficient or imprecise data. Inconsistency in recommendations for some outcomes and research gaps were identified.

Conclusions. Our findings may serve as a helpful tool in planning further research, preventive actions against important diet-related diseases, and guidelines improvement.

INTRODUCTION

Emerging evidence suggests that nutrition during early life may have consequences extending into adulthood. The pathogenesis of a number of diseases, including so- called non-communicable diseases (NCD) (i.e., non-infectious and non-transmissible diseases among people) such as cardiovascular disease, obesity, diabetes mellitus, allergy and other immune diseases, some forms of cancer, mental health problems, osteoporosis, chronic respiratory disease, and musculoskeletal conditions, has been linked, among other factors, to maternal and early infant diet and nutrition (Agostoni et al., 2013; Barouki et al., 2012).

EarlyNutrition (www.project-earlynutrition.eu) is an international research project, which is sponsored by the European Union 7th Framework Programme. The project's objectives include providing improved evidence of the effects of early nutrition on metabolic programming and their consequent health impacts. This project brings together an international consortium of renowned experts in various research fields. The aim is to form a multilateral partnership for the enhancement of knowledge on early nutrition and metabolic programming and its impact on obesity and the risk of related disorders in adulthood.

The objective of this paper, prepared as part of the EarlyNutrition project, is to summarize, by performing a systematic review, current standards, recommendations, guidelines, and regulations on nutrition in healthy, term infants and children aged 1 to 3 years, with special emphasis on EarlyNutrition project objectives. These include the effects of early nutrition on later health with respect to cardiovascular disease, hypertension, overweight or obesity, metabolic syndrome, diabetes, or glucose intolerance. Furthermore, another objective was to identify potential research gaps that will help to develop research agendas.

METHODS

Review protocol

The methods of each stage of this review were specified in advance, discussed during the EarlyNutrition meetings, and documented. However, formally, the review protocol was not registered.

Terminology

A number of terms such as ‘standards,’ ‘recommendations,’ ‘guidelines,’ ‘regulations,’ as well as ‘position papers’ and ‘opinions’ exist. There is a distinction between these terms; however, they are commonly used interchangeably. Moreover, some of them have the power of law in some, albeit not all, countries. For this review, the decision was made to use the terminology used by the authors of the original publication. If all publications are considered jointly, the term ‘documents’ is used.

Criteria for eligibility

Documents relating to the nutrition of healthy, term infants and young children aged 1 to 3 years were included in this review. Only English-language documents developed by and recognized by international and national societies and organizations, were included. Position papers, scientific reports, and commentaries were also considered for inclusion. To ensure that the most up-to-date documents were included, inclusion was limited to papers published in the years 2008-2013 (January). Different aspects of nutrition that were the subject of identified documents were classified as follows: (1) Breastfeeding; (2) Formula-feeding; (3) Complementary feeding; (4) Dietary carbohydrates and fiber; (5) Dietary proteins; (6) Energy intake; (7) Fats and fatty acids (including LC-PUFA); (8) Meal patterns or food habits; (8) Minerals (calcium, iron, potassium,

sodium); (9) Probiotics and prebiotics; (10) Vitamins (vit. B group, folate, vit. C, vit. A, vit. D, vit. E, vit. K); and (11) Others (water, plant foods).

The document had to relate to the effectiveness and/or safety of those dietary exposures/interventions and their influence on health outcomes as defined by the authors. Special emphasis was placed on outcomes related to the EarlyNutrition objectives: cardiovascular disease, hypertension, overweight and/or obesity, metabolic syndrome, diabetes, or glucose intolerance.

Criteria for exclusion

Documents focused exclusively on prevention or treatment of a particular disease, such as allergic diseases or vitamin K deficiency bleeding, that were not related to the outcomes mentioned above, were excluded. Also, documents dedicated to a local community, without national or international outreach, were eliminated. Additionally, we did not consider for inclusion documents developed for special populations (such as preterm infants, children with chronic diseases) as well as those not meeting our age criteria (infants and children aged 1 to 3 years).

Search strategy

The documents of interest were identified through searching bibliographic databases, i.e., Ovid MEDLINE and selected guideline databases or websites of relevant professional organizations that may have produced guidelines. In addition, references were obtained by consultation with experts in the field (partners of the EarlyNutrition project). All databases (provided in **Table 1**), if possible, were searched with a combination of the phrases (infant* or child*) AND (feeding or nutrition). Alternatively, they were simply hand searched, which was also the case for some

(listed in **Table 1**) websites of relevant professional bodies and associations. In our search strategy for Ovid MEDLINE, we used a combination of groups of key words (free text and MESH terms) related to our target population, different nutritional components, and the type of preferred documents. The detailed search strategy is provided in **Table 2.**

Guidelines selection

Two reviewers (BP, BZ) independently screened all provided sources and titles, abstracts, and full text documents for possible inclusion. Discrepancies were resolved by discussion, when necessary, by a consultation with another team members, until consensus was reached.

Data collection process

Three teams, each consisting of two independent reviewers (MV&SK, BP&BZ, PC&JC), were involved in the data extraction process. Summary tables were developed to present recommendations of different scientific bodies referring to each, previously stated dietary component. The extracted data included references (title, authors, year of publication), a brief recommendation and the population to which it is referring, the level of evidence (if stated by the authors), the impact on defined health outcomes (if assessed by the authors), the type of the report, and authors' suggestions for further research/identified research gaps. Afterwards, all extracted data were checked independently by two co-authors (BP, BZ). Discrepancies were resolved by discussion and, when needed, by a consultation with members of the group.

Assessment of methodological quality

We did not perform any formal methodological assessment of the included guidelines' quality, and we did not attempt to evaluate the level of evidence of each recommendation if not done so by the authors.

Determining research gaps

We extracted research gaps, associated to EarlyNutrition outcomes, recognized by the authors of the identified documents.

RESULTS

Almost 2500 records were screened after applying the search strategy. The precise number of records screened remains undetermined; this is related to the hand searching through different websites of the scientific bodies without the number of publications provided there. From the initially identified articles, we found 156 publications that required further full text evaluation. Of these, we selected 42 papers that met our inclusion criteria. However, only some of them addressed the outcomes of interest to us. **Figure 1** shows a detailed description of the different stages of data identification and the selection process. **Tables 1S to 12S (see online Supporting Information)** present summaries of all relevant recommendations referring to different nutrient components or feeding patterns. **Table 3** presents a summary of research gaps, as provided by the authors of the original documents.

Summary of the recommendations and its relation to selected outcomes

Breastfeeding (Table 1S)

Fourteen of the included documents addressed breastfeeding as a subject of recommendations and as an important dietary component for many health outcomes (NHLBI, 2011; ESPGHAN, 2009; Perinatal Services, 2012; AAP, 2012; SACN, 2011; August et al., 2008; IFJWG, 2012; ABMBD, 2008; Quak et al., 2008; NICE, 2008; WHO, 2011; SACN, 2011a; EFSA, 2009; IOM, 2011; Koletzko et al., 2008). However, only three of these documents assessed and graded the quality of the provided recommendations (NHLBI, 2011; Perinatal Services, 2012; August et al.,

2008). In most cases, breastfeeding was recommended as the preferred feeding for all infants. There is a consistency across the guidelines that exclusive breastfeeding for around 6 months is a desirable goal. Partial breast-feeding as well as breast-feeding for shorter periods of time are also valuable. However, the optimal age for introduction of complementary foods (between four to six months versus after six months) in exclusively breast fed infant remains controversial. After breastfeeding initiation, while gradually introducing complementary feeding, breastfeeding should last – depending on the authors of the recommendations – until the age of 1 year or more (AAP, 2012; NHLBI, 2011; IFJWG, 2012; ABMBD, 2008) or as long as the mother and child wish to do so (ESPGHAN, 2009; NICE, 2008).

Early Nutrition outcomes

Cardiovascular disease. The relationship between breastfeeding and cardiovascular disease prevention was addressed in four documents (SACN, 2011; NHLBI, 2011; ESPGHAN, 2009; Perinatal Services, 2012). Only the National Health, Lung and Blood Institute (NHLBI) found breastfeeding to be beneficial with a strong, sustained effect on cardiovascular health (NHLBI, 2011). The remaining three documents summarized the current evidence as inconclusive (SACN, 2011; ESPGHAN, 2009; Perinatal Services, 2012).

Hypertension, overweight/obesity, metabolic syndrome, diabetes. There was consistency among the recommendations from the included studies regarding the positive influence of breastfeeding on the prevention of hypertension (SACN, 2011; NHLBI, 2011; ESPGHAN, 2009; Perinatal Services, 2012; ABMBD, 2008), type 1 diabetes (SACN, 2011; AAP, 2012; ESPGHAN, 2009; Perinatal Services, 2012; ABMBD, 2008) or type 2 diabetes (SACN, 2011; Perinatal Services, 2012; ABMBD, 2008), and overweight or obesity (SACN, 2011; NICE, 2008; IOM, 2011). The

clinical practice guidelines developed by the Endocrine Society stated that there is a strong recommendation to support breastfeeding for a minimum of 6 months to prevent obesity (August et al., 2008). The guidelines were also consistent with regard to the effect of breastfeeding on the reduction of serum cholesterol levels in adulthood (SACN, 2011; NHLBI, 2011; Perinatal Services, 2012; ABMBD, 2008).

Formula Feeding (Table 2S)

Only a limited number of identified recommendations focused on infant formula feeding (NHLBI, 2011; IFJWG, 2012; Bhatia et al., 2008; CPS, 2009). Generally, these recommendations emphasized that formula feeding is an alternative, second choice feeding method for those children who cannot be breastfed or given human milk. Also it was emphasized that the indications for soy-based formula use are very limited (IFJWG, 2012; Bhatia et al., 2008; CPS, 2009).

Early Nutrition outcomes

Blood pressure. According to the NHLBI, supplementation of infant formula with polyunsaturated fatty acids (PUFA) is associated with lower blood pressure (NHLBI, 2011).

Complementary feeding (Table 3S)

The optimal timing of complementary foods introduction was discussed in most of the included documents. In general, complementary food should be introduced into the infant diet within the range of 4-6 months of age (AAP, 2012; NHLBI, 2011; ESPGHAN, 2009; NICE, 2008; EFSA, 2009; IOM, 2011; ESPGHAN, 2008). The need for introduction of food rich in iron (AAP, 2012; ESPGHAN, 2009; IFJWG, 2012; ESPGHAN, 2008) and zinc (AAP, 2012) was also emphasized. With regard to gluten introduction, the European Society for Pediatric Gastroenterology,

Hepatology and Nutrition (ESPGHAN) recommended against early (<4 months) and late (≥7 months of age) gluten introduction (ESPGHAN, 2009; ESPGHAN, 2008). Similarly, the European Food and Safety Agency (EFSA) advised to introduce gluten no later than by 6 months of age (EFSA, 2009). Both organizations stress the benefit of maintaining a breast milk supply at the time of gluten introduction. The American Academy of Pediatrics (AAP) emphasized the critical role of breastfeeding overlap at the time of gluten introduction in celiac disease prevention (AAP, 2012). In contrast, according to the Scientific Advisory Committee on Nutrition (SACN), there is insufficient evidence to support recommendations on gluten introduction into the diets of infants beyond 3 completed months of age or no later than 6 months of age with respect to the subsequent risk of celiac disease and type 1 diabetes (SACN, 2011b).

Early Nutrition outcomes

Cardiovascular disease. The relationship between complementary feeding and cardiovascular disease prevention was assessed in three documents (SACN, 2011; EFSA, 2009; ESPGHAN, 2008). According to SACN, it is unclear whether there is any independent effect of the early introduction of complementary feeding and diet quality on cardiovascular outcomes in adult life (SACN, 2011). Similarly, ESPGHAN stated that in regard to cardiovascular outcomes, no specific recommendations can be made for choices or composition of complementary feedings (ESPGHAN, 2008). Additionally, according to EFSA's scientific opinion, the timing of the introduction of complementary food may affect the rate of length and weight gain of a child and indirectly influence the risk of cardiovascular disease in adult life (EFSA, 2009).

Hypertension, overweight/obesity. According to ESPGHAN, cow's milk introduction before 12 months can affect linear growth and further can negatively influence blood pressure and the risk

of obesity, but the evidence is not convincing (ESPGHAN, 2008). With respect to overweight and obesity, there is a consensus among scientific bodies that the evidence on the effects of complementary food introduction and the risk of obesity is inconsistent, with some data suggesting the possibility of an indirect action through the impact on growth velocity (SACN, 2011; EFSA, 2009; IOM, 2011; ESPGHAN, 2008).

Diabetes and glucose intolerance. As per the EFSA document, there is no evidence to support an influence of age of introduction of complementary foods on the development of type 2 diabetes (EFSA, 2009). According to EFSA and ESPGHAN, the timing of gluten introduction influences the risk of developing type 1 diabetes (EFSA, 2009; ESPGHAN, 2008). In contrast, SACN concluded that the evidence to support a certain time of gluten introduction in relation to developing type 1 diabetes is insufficient (SACN, 2011b).

Dietary carbohydrates (Table 4S)

Carbohydrate intake from the diet was assessed in three documents (NHLBI, 2011; EFSA, 2010; USDA, 2010). The recommended percentage of total caloric intake from carbohydrates was estimated as ranging from 45% to 65%. There was a consistency among recommendations to limit intake of rapidly absorbed carbohydrates and simple sugars (the main sources of which are sugar-sweetened beverages) (NHLBI, 2011; USDA, 2010; ESPGHAN, 2011) in favor of slowly absorbed carbohydrates (ESPGHAN, 2011).

Early Nutrition outcomes

Cardiovascular disease, overweight/obesity, type 2 diabetes. Although outcomes such as cardiovascular disease, raised serum lipids, obesity, and diabetes mellitus were addressed in regards to the total carbohydrate intake and glycemic index in EFSA's scientific opinion (EFSA,

2010), all conclusions (mostly based on studies performed in adults) were made for the general population. No consistent relationship between total or glycemic carbohydrate intake, as well as between dietary glycemic index reduction and cardiovascular disease risk, was found. The guidelines consistently recommended a decrease in the use of sweet beverages (and rapidly absorbed carbohydrates) for prevention of overweight and/or obesity (NHLBI, 2011; EFSA, 2010; USDA, 2010; ESPGHAN, 2011). However, according to the Institute of Medicine (IOM), no association was found between 100% juice use and further increased risk of overweight and/or obesity (IOM, 2011).

Fiber (Table 4S)

As shown in **Table 4S,** different recommended intakes of fiber for children were proposed by the authors of three documents (NHLBI, 2011; EFSA, 2010; USDA, 2010), with the important conclusion made by the EFSA Panel that there is limited evidence to set adequate intakes of fiber for children (EFSA, 2010).

Early Nutrition outcomes

Dietary fiber intake is inversely associated with energy density and increased levels of body fat, according to the NHLBI (NHLBI, 2011). Moreover, the authors of "Dietary Guidelines for Americans" suggest that in children older than 2 years of age, consumption of foods high in fiber may help reduce the risk of obesity, cardiovascular disease, and type 2 diabetes (USDA, 2010). However, based on the statement by SACN (SACN, 2008), there is no evidence to suggest an association between dietary fiber intake and weight control in children.

Proteins (Table 5S)

Recommendations regarding the percentage of total caloric intake from protein (in children older than 1 year of age) suggested the range of intake from 5% to 20% (NHLBI, 2011; USDA, 2010). EFSA provided the average daily requirement per kg of body weight for different age groups (also infants) (**Table 5S)** (EFSA, 2012).

Early Nutrition outcomes

Overweight/obesity, insulin sensitivity. There is full agreement between the different scientific bodies that there is insufficient evidence to conclude that higher protein intake in infancy increases the risk of obesity in later life (SACN, 2011; ESPGHAN, 2011; EFSA, 2012). Similar conclusions with regards to insulin sensitivity and glucose tolerance were made by EFSA (EFSA, 2012).

Energy (Table 6S)

Energy requirements for various age and sex groups are shown in detail in **Table 6S** (NHLBI, 2011; SACN, 2011a; IOM, 2011; USDA, 2010; ESPGHAN, 2011; EFSA, 2013).

Early Nutrition outcomes

Overweight/obesity. Energy intake should be balanced (i.e., by reducing consumption of energy-dense foods) to meet individual needs in order to maintain a healthy body weight (SACN, 2011a; IOM, 2011; USDA, 2010; ESPGHAN, 2011). Energy balance should be individually determined adjusting for energy expenditure and growth (ESPGHAN, 2011). Presentation of single nutrient intakes (fats, carbohydrates, proteins) per estimated energy requirements, as in the NHLBI document (NHLBI, 2011), is helpful in fulfilling this recommendation.

Fats and fatty acids (Table 7S)

For recommendations regarding fat intake (including long-chain polyunsaturated fatty acids, LC-PUFA) in different age groups, see **Table 7S** (NHLBI, 2011; USDA, 2010; EFSA, 2010a, FAO, 2010). We have noted inconsistency between the NHLBI (NHLBI, 2011) recommendation on total fat quantity (no restrictions in infants younger than 1 year of age) and both the Food and Agriculture Organization (FAO) (FAO,2010) and EFSA (EFSA, 2010a) (recommending a gradual reduction of fat intake starting from 6 months of life).

In regard to LC-PUFA, according to the EFSA panel, children aged 2-18 years should be advised to consume either 1 to 2 fatty fish meals per week or a 250 mg eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) as a supplement. Adequate intake of DHA for infants 7-24 months of age has been established as 100 mg daily. The need for adequate PUFA intake is also suggested by other authors (NHLBI, 2011; USDA, 2010; FAO, 2010). Additionally, the World Association of Perinatal Medicine Working Group (Koletzko et al., 2008) strongly supports supplementation of infant formula with LC-PUFA (docosahexaenoic acid, eicosapentaenoic acid). However, in regards to the development of cognitive functions, ESPGHAN emphasizes that there is no evidence to support a favorable effect of LC-PUFA supplementation in addition to dietary intake in children aged over 2 years (ESPGHAN, 2011a). Scientific bodies are consistent in their recommendations to limit saturated fatty acids (SFA) intake in children's diets (NHLBI, 2011; USDA; 2010; EFSA, 2010a; FAO, 2010).

Early Nutrition outcomes

Cardiovascular disease, hypertension. The adherence to acceptable total fat intake ranges is associated with a lower risk of cardiovascular disease according to the "Dietary Guidelines for Americans" (USDA, 2010). The authors emphasize that even more important than total fat intake

is the type of fat consumed. Reducing the consumption of saturated fatty acids by replacing them with PUFA and possibly monounsaturated fatty acids (MUFA) is known to modify the risk of cardiovascular disease. In addition, keeping the intake of trans fatty acids as low as possible by limiting the intake of calories from solid fats is another factor that is known to modify the risk of cardiovascular disease. These conclusions are in line with other scientific bodies' statements (NHLBI, 2011; EFSA, 2010a; FAO, 2010).

With regards to infants, according to the World Association of Perinatal Medicine (Koletzko et al., 2008), adding DHA and arachidonic acid (AA) to infant formula *'might have lasting effects on reduced blood pressure and cardiovascular risk'.* It was also concluded that in the general population, n-3 LC-PUFA have a beneficial effect on blood pressure (EFSA, 2010a; FAO, 2010).

Overweight/obesity. The ESPGHAN stated that an association between total fat intake and specific dietary lipids (in children >2 years of age) and obesity development is possible. However, no recommendations on fat quantity or quality can be made because of the paucity of data (ESPGHAN, 2011). The Food and Agriculture Organization (FAO) (FAO, 2010) also argues that there is insufficient evidence that intake of mono- or poly-unsaturated fatty acids is connected with a decreased obesity risk. In line with this, according to the EFSA, there is no evidence that n-3 PUFA (at habitual intakes) has a clear impact on energy balance (EFSA, 2010a). Moderate total fat intake (within the recommended ranges of total energy intake percent), although suggested to be associated with prevention of excessive weight gain in some documents (NHLBI, 2011; EFSA, 2010a), according to the FAO cannot be considered effective due to inconclusive evidence (FAO, 2010).

Metabolic syndrome/lipoprotein profile. A positive influence in regard to total cholesterol and LDL levels is described in FAO (FAO, 2010), NHLBI (NHLBI, 2011) and EFSA (EFSA, 2010a) recommendations when saturated fatty acids and trans fatty acids are replaced with PUFA.

Diabetes and insulin sensitivity. A lower risk of insulin resistance can be attained when following the NHLBI proposed dietary composition (NHLBI, 2011). In order to decrease the risk of developing type 2 diabetes (based on adult studies), saturated fatty acids should be limited and replaced with PUFA according to the FAO (FAO, 2010). Data on consumption of monounsaturated fatty acids is inconsistent in regard to this outcome point (FAO, 2010). The EFSA concluded that there is inconsistent data that fatty acids influence insulin sensitivity. Also, the relationship between fatty acids intake and the risk of type 2 diabetes is unclear (EFSA, 2010a).

In summary, it is crucial to emphasize that the above conclusions regarding fat intake mainly apply to the general population and are based on studies performed in different age groups, very often in adults only. The influence of the dietary fats on lipoprotein levels in younger children remains uncertain. However, the FAO statement '*although there is no specific data from long term studies on the relationship between fatty acid intake and chronic disease prevention from children the assumption is that children also benefit from lower saturated fat and higher PUFA intakes'* may be followed.

Meal patterns, food habits (Table 8S)

Among the included documents, there were four emphasizing meal patterns as important to health effects later in life (NICE, 2008; IOM, 2011; USDA, 2010; ESPGHAN, 2011).

Early Nutrition outcomes

Cardiovascular disease. The use of the DASH (Dietary Approaches to Stop Hypertension) diet (that consists of vegetables, fruits, low-fat or fat-free dairy products, whole grains, poultry, seafood, nuts and includes lower intake of sodium, red and processed meats, sweets, and sugar-sweetened beverages) is associated with lower blood pressure and a reduced risk of cardiovascular disease in the general population (NHLBI, 2011; USDA, 2010; FAO; 2010).

Overweight/obesity. The "Dietary Guidelines for Americans" (USDA, 2010), ESPGHAN (ESPGHAN, 2011), and IOM (IOM, 2011) are consistent in their positions that particular meal patterns can contribute to obesity prevention; however, there are no specific studies to confirm this correlation (IOM, 2011). The NHLBI suggested compliance with CHILD-1 (The Cardiovascular Health Integrated Lifestyle Diet) (for details, see **Table 8S**), together with monitoring of the body mass index and dietary intake, as the only necessary dietary interventions to prevent obesity (NHLBI, 2011).

Diabetes and insulin sensitivity. Eating patterns that are low in energy density can be associated with a lower risk of type 2 diabetes in adults according to the "Dietary Guidelines for Americans" (USDA, 2010).

Minerals (Table 9S) and Vitamins (Table 10S)

Minerals

Identified guidelines mainly focused on the sodium, calcium, and iron intake. Limitation of sodium intake in children is one of the most important messages. Specific recommendations and adequate intakes for these and some other minerals (potassium, zinc, fluoride, magnesium, phosphorus, selenium, copper) are presented in detail in **Table 9S** (USDA, 2010; IOM, 2012; Baker et al., 2010; SACN, 2010; WHO, 2012; WHO, 2012a).

Vitamins

Vitamin D supplementation is the subject of the majority of identified documents. There is a consistency among recommendations for a daily dose of vitamin D supplementation (400 IU) in breast-fed and partially breast-fed infants (AAP, 2012; ESPGHAN, 2009; IFJWG, 2012; NICE, 2008; IOM, 2012; Wagner et al., 2008). Recommended daily intakes of vitamin D and some other vitamins in children 1-3 years of age are provided in the "Dietary Guidelines for Americans" (USDA, 2010). In regards to vitamin A supplementation, it is recommended by WHO in children > 6 months of age, but only in settings where vitamin A deficiency is a public health problem (WHO, 2011; WHO 2011a; WHO 2011b).

Early Nutrition outcomes

Cardiovascular disease, hypertension, overweight/obesity, diabetes. There is an agreement between the different scientific bodies that limitation of sodium intake in children has a beneficial effect on blood pressure and also indirectly may influence the risk of associated cardiovascular disease (SACN, 2011; NHLBI, 2011; USDA, 2010; WHO, 2012a). On the other hand, according to WHO, however based on limited data, an increase in potassium intake, especially from dietary sources, prevents a rise in blood pressure (WHO, 2012). Although the association between iron intake (in particular, excess of iron) and the risk of cardiovascular disease has been considered, limited data from studies in adults do not support this hypothesis. No conclusions can be made for children (SACN, 2010). According to the IOM document on calcium and vitamin D intake, current evidence is inconsistent in regards to all Early Nutrition outcomes (IOM, 2012). This is in line with the ESPGHAN position on calcium and dairy product intake in reference to the development of overweight and/or obesity (ESPGHAN, 2011).

According to the AAP, some data may suggest that early supplementation with vitamin D (in infants and young children) can decrease the incidence of type 1 diabetes (Wagner et al., 2008).

Probiotics and prebiotics (Table 11S)

Specific recommendations regarding prebiotics and probiotics use in children are presented in **Table 11S** (Guarner et al., 2012; Thomas et al., 2010; CPS, 2012; ESPGHAN, 2011b). Importantly, insufficient evidence of clinical benefits does not allow one to recommend routine supplementation of infant milk formula with prebiotics, probiotics, or synbiotics (nutritional supplements combining probiotics and prebiotics).

Early Nutrition outcomes

There is no evidence to support the use of probiotics/prebiotics to reduce the risk of cardiovascular disease (Guarner et al., 2012) or obesity (ESPGHAN, 2011).

Others (Table 12S)

The ESPGHAN Committee on Nutrition recommended plant-based foods as possible contributors to a well-balanced diet (ESPGHAN, 2011). Additionally, SACN recommended against the use of unfounded claims for breast milk substitutes in the diets of infants aged 6 months and more (SACN, 2008a). In regards to water, daily adequate intakes according to the child's age are provided in the EFSA scientific opinion (EFSA, 2010b). Two other documents recommended consumption of water or calorie-reduced beverages to meet total water needs in children (IOM, 2011; USDA, 2010).

Early Nutrition outcomes

According to the IOM, drinking water as an alternative to sugar-sweetened beverages plays a positive role in reducing obesity risk (IOM, 2011).

Research gaps

Table 3 summarizes research gaps extracted from the included documents. The most important recommendations for further research include the following: timing and type of complementary feeding; duration of breastfeeding and its association with the risk of cardiovascular disease; the influence of energy balance (dietary intake, energy expenditure) on growth patterns; the role of dietary fat quality and quantity assessed in the pediatric population; the role of vitamin D supplementation in non-skeletal health outcomes; and the role of protein and specific amino acids intake on weight gain and body composition.

DISCUSSION

Principal findings

The EarlyNutrition project was designed to answer clinically important questions and to help in building foundations of future evidence-based recommendations. To our knowledge, this is the first systematic review of current documents developed by different organizations on the nutrition of infants and young children, as well as the effects of early nutrition on later outcomes, such as cardiovascular disease, hypertension, overweight or obesity, metabolic syndrome, diabetes, or glucose intolerance. The strongest and most consistent evidence for a protective, long-term effect of early nutrition was documented for breastfeeding. Other recommended actions, such as limitation of sodium and rapidly absorbed carbohydrates intake, use of a specific meal pattern, reducing the consumption of saturated fatty acids by replacing them with polyunsaturated fatty acids, and lowering the intake of trans fatty acids, also seem to have a beneficial effect on reducing the risk of obesity and/or related diseases. However, of the 42 included documents, many did not evaluate long-term outcomes of interest to us or reported

insufficient data to allow one to draw conclusions. Some discrepancies in recommendations by the different organizations were noticed. Most of the documents present the recommendations in a narrative form, rather than short statements with information on grade of evidence and corresponding population. A number of documents identified research gaps. However, the criteria used were variable and generally unclear. None of the included documents used standardized methods for identifying or prioritizing research gaps.

Strengths and weaknesses

One of the major strengths of our review was the comprehensive search for eligible documents (high sensitivity of search strategy). Still, there are several limitations of this review. First, we searched only for documents written in English. Therefore, there is the possibility that high quality documents written in other languages might have been missed (possible language bias). Second, the lack of use of any critical appraisal tool for guidelines quality assessment could be an important limitation. Also, we did not assess the quality of evidence that the guidelines are based upon. Nevertheless, if available, we extracted the proposed by the authors' level of evidence for recommendations. Third, current evidence on the long-term effects of early nutrition is based in part on associations. For example, increased blood pressure in childhood implicates a high risk for hypertension in adulthood, and reduction of sodium intake in children reduces blood pressure. The conclusion made in the guideline was that reduced intake of sodium in children can indirectly be connected with prevention of hypertension in adults (WHO, 2012a). It is not possible on the basis of the associations alone to determine whether the characteristics of the diet or lifestyle are a result of the disease process or whether the characteristics of the diet or lifestyle cause the disease. Fourth, often studies in the pediatric population were not available,

and the recommendations were made based on evidence from studies performed in adults. Caution is needed when interpreting such data. Fifth, to ensure that only the most up-to-date documents were included, inclusion was limited to papers published in the last 5 years. While making this decision, we followed the example of the American Academy of Pediatrics. All AAP policy statements automatically expire 5 years after publication unless reaffirmed. Some authors are even more strict and recommend that recommendations should be re-evaluated every three years (Shekelle et al., 2012). We acknowledge that, as a consequence, some high-quality documents such as those developed by AAP (Barlow et al., 2007) or WHO/FAO (WHO/FAO; 2012) were not included in our systematic review.

Research gaps

Generally, evidence on long-term effects of dietary interventions in regard to EarlyNutrition outcomes is lacking. However, the authors of included documents recognize the importance of these outcomes. Accurate recording of children's dietary intake and characterization of their dietary habits is necessary. In the future, validated clinical outcome measures assessing the effects of early nutritional interventions should be used in well-designed and carefully conducted randomized controlled trials, with relevant inclusion/exclusion criteria and adequate sample sizes.

CONCLUSIONS

This systematic review of current documents developed by different organizations on the nutrition of infants and young children, as well as the effects of early nutrition on later outcomes, such as cardiovascular disease, hypertension, overweight or obesity, metabolic syndrome, diabetes, or glucose intolerance documents show that many aspects of nutrition need further

elucidation, especially in regards to the long-term effects. This review can form a foundation for further research based on gaps provided by the authors of recommendations and identified during the review process.

ACKNOWLEDGEMENTS

The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013), project EarlyNutrition under grant agreement n°[289346].

We would like to thank Ms. Kath Wright from Centre for Reviews and Dissemination, The University of York, for valuable help in preparing search strategy.

We would like to thank dr Janis Baird and prof. Lucilla Poston for valuable comments to final publication.

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Table 1. Sources searched

SIGN Guidelines http://www.sign.ac.uk/
National Guideline Clearinghouse http://www.guidelines.gov/
National Coordinating Centre for Health Technology Assessment http://www.hta.ac.uk/
NICE Guidelines http://www.nice.org.uk/
Health Services/Technology Assessment Texts (HSTAT) http://www.ncbi.nlm.nih.gov/books/NBK16710/
TRIP http://www.tripdatabase.com
NHS Evidence http://www.evidence.nhs.uk/default.aspx
NHS Clinical Knowledge Summaries (formerly PRODIGY) http://www.cks.nhs.uk/home
Health Systems Evidence: http://www.healthsystemsevidence.org/
HSRProj Information about ongoing health services research and public health projects from National Library of Medicine http://wwwcf.nlm.nih.gov/hsr_project/home_proj.cfm

Websites of relevant professional bodies and associations that may have produced guidelines:

European Society of Paediatric Hepatology, Gastroenterology and Nutrition (ESPGHAN)

http://www.espghan.med.up.pt/

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)

http://www.naspghan.org

American Academy of Pediatrics (AAP)

http://www.aap.org/

World Health Organization (WHO)

http://www.who.int/publications/guidelines/en/index.html

Institute of Medicine (IOM)

http://www.iom.edu/

Scientific Committee on Nutrition (SACN)

http://www.sacn.gov.uk/

European Food and Safety Agency (EFSA)

http://www.efsa.europa.eu/en/publications.htm

Table 2. Medline search strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
1. infant food/
2. infant formula/
3. bottle feeding/
4. breast feeding/
5. Infant feed$.ti,ab.
6. (Breastfeed$ or breast feed$).ti,ab.
7. Bottle feed$.ti,ab.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (diet$ or food$ or eat or eats or eaten or eating or nutrition$ or fruit$ or vegetable$ or nutrient$ or vitamin c or thiamin or niacin or folate$ or micronutrient$ or macronutrient$ or multivitamin$ or folic acid or magnesium or selenium or zinc or pyridoxine or riboflavin or nicotinic acid or dietary salt).ti,ab.
10. diet/ or exp food/ or nutrition/ or exp fruit/ or vegetables/ or dietary iron/ or dietary calcium/ or exp dietary fats/ or exp dietary proteins/ or exp dietary carbohydrates/ or exp vitamins/ or exp riboflavin/ or exp nicotinic acids/ or exp pyridoxine/ or zinc/ or folic acid/ or magnesium/ or selenium/ or sodium, dietary/ or exp energy intake/
11. 9 or 10
12. (baby or babies or infant$ or infancy or child$).ti,ab.

13. Child, preschool/ or infant/ or child/
14. 12 or 13
15. 11 and 14
16. 8 or 15
17. exp asia/ or exp africa/ or exp south america/ or exp developing countries/
18. 16 not 17
19. exp animals/ not humans.sh.
20. 18 not 19
21. exp practice guideline/
22. Health Planning Guidelines/
23. guideline$.ti.
24. (practice adj3 parameter$).ti,ab.
25. clinical protocols/
26. guidance.ti,ab.
27. care pathway$.ti,ab.
28. critical pathway/
29. (clinical adj3 pathway$).ti,ab.
30. consensus development conference.pt.
31. consensus development conference nih.pt.
32. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 20 and 32

34. Limit 33 to last 5 years

Table 3. Research gaps identified by the authors of the guidelines

ACCEPTED MANUSCRIPT

References	Further research/ research gaps (if identified by the authors)	Notes/Type of dietary intervention discussed
SACN, 2011	• Large, longitudinal cohort studies capable of characterizing relationships between early life nutritional exposures and adult chronic disease risk should incorporate measures of pre-conceptional nutritional status, fetal and placental growth, offspring body composition and metabolic competence. Such data will better characterize patterns of pre- and post-natal growth associated with greatest risk of adult chronic disease. • Clinical trials investigating changes to the composition of infant formula should incorporate follow-up to capture long-term outcomes • Experimental studies in animal models required to expand understanding of the mechanisms that explain observed associations between nutrition in early life and subsequent chronic disease outcomes. • Little human evidence linking long term outcome to the effect of restricting intake of specific	• Breastfeeding • Complementary feeding • Carbohydrates • Fats and fatty acids • Proteins • Minerals • Vitamins

	nutrients in fetal or early postnatal life. • Influence of early introduction of solid foods and diet quality on cardiovascular risk and cardiovascular outcome in later life is unclear.	
ESPGHAN, 2009	• For countries with a low infectious disease burden, the optimal duration with respect to health outcomes of any breastfeeding after introduction of complementary feeding is uncertain because of a lack of data.	• Breastfeeding
Perinatal Services, 2012	• Associations between breastfeeding and cardiovascular diseases; breastfeeding and the risk of cardiovascular diseases later in life; and breastfeeding and infant mortality in developed countries were unclear; further studies are advised.	• Breastfeeding
Quak et al., 2008	• A definition for obesity in children <24 months is urgently needed. • Primary prevention approaches for tackling obesity are also needed. • Improved assessment methodologies for accurately assessing the role of diet and physical activity	None

	in the development of obesity and its comorbidities, as well as for its prevention and treatment, are needed.	
WHO, 2011	• Further research is needed to determine the appropriate cut-offs for the indicators of retinol status in the first 6 months of life.	• Vitamins
SACN, 2011	• Limited data for infants and children are available to enable estimation of energy requirements. • Further data on the relationship between energy intake and the quality and quantity of growth in infants, regardless of the mode of feeding, should be collected. • Understanding of the potential interaction of diet composition and physical activity in body weight regulation and the development and maintenance of obesity should be improved.	• Energy
IOM, 2011	• Research on the effects of early introduction of complementary foods and obesity risk is inconsistent.	• Complementary feeding
NICE, 2008	• Pre-school children's diets are still an area of concern and should be addressed. • Research into the acceptability of dietary and lifestyle interventions to improve the vitamin D status	• Meal patterns • Vitamins

	of mothers and children aged up to 5 years, particularly those from vulnerable groups, is needed. This should also assess the relative contribution made by exposing the skin to ultraviolet light and dietary supplements.	
EFSA, 2009	• There are numerous publications that discuss the timing of initiating complementary feeding with regard to breast-fed infants, while the literature on non-breast-fed infants is limited.	• Complementary feeding
Koletzko, et al., 2008	• Short- and long-term effects of LC-PUFA status during infancy according to inter-individual differences, such as genetic variation in fatty acid desaturase activities or gender, should be determined. • Examination of growth, body composition and bone mineralization, visual and cognitive development, as well as effects on immune outcomes and cardiovascular function, should be done. • Evaluation of different amounts of LC-PUFA, and the specific effects of arachidonic acid supply, with sufficient duration of intake, adequate sample sizes, and standardized methodology for outcome measurements should be done. • Consideration of various levels of DHA in order to determine possible dose-response relationships and to elucidate potential immediate and long-term benefits in infant formula studies should be done.	• Fats and fatty acids

	• Dose-response studies of LC-PUFA intake during the second 6 months of life are needed. • Development and evaluation of simplified measures of dietary supply and of LC-PUFA status should be done.	
ESPGHAN, 2011	• Exploration of the role of specific amino acids on weight gain and body composition is needed. • Further pediatric data are needed on the effects of total fat consumption and the potential role of dietary fat quality and composition on the development of childhood obesity.	• Proteins • Fats and fatty acids
EFSA, 2013	• The impact of differences in body composition (especially gains in lean or fat mass during the first year of life) on resting energy expenditure (REE) in relation to age, ethnicity, and other factors needs to be determined. • Body composition in infants in relation to energy intake needs to be determined. • For a more precise estimate of energy requirements at the European Union (EU) level, the Panel suggests generating and collecting more doubly labeled water (DLW) data, in conjunction with REE measurements, in healthy adults and children in the EU who are representative of various geographical regions, and including individuals of all ages with a broad range of Physical Activity Levels (PALs) corresponding to well-defined lifestyles.	• Energy

FAO, 2010	**RESEARCH NEEDS FOR CHILDREN 2-18 YEARS** • Further systematic research is needed to provide a sound scientific basis for formulating specific intake values for n-3 LCPUFA in children 2-18 years of age (relevant public health outcomes include future risk of CVD and metabolic syndrome, optimal mental development and behavior, and immune response). • Age-specific information on fatty acids status based on biological markers is required (because assessment of dietary intake is always inaccurate). • Age-specific effects of different fatty acid intakes and dosages on relevant endpoints should be assessed in controlled intervention studies. • Establishing the effect of different doses of individual fatty acids, and of different combinations and ratios of PUFA, on well-defined and quantifiable outcomes of public health significance should be done. • Potential adverse effects of recommending increased dietary intakes of EPA and DHA or of fatty fish should be assessed. • Consider short- and long-term effects of genetic variation in fatty acid desaturase activities and the respective effect of LCPUFA intake prior to and during pregnancy, lactation, and infancy.	• Fats and fatty acids

	• Supplementation studies should aim to examine growth, body composition and bone mineralization, visual and cognitive development, as well as effects on immune outcomes such as allergy and inflammatory disorders and cardiovascular function. • Studies evaluating different amounts of LCPUFA, and the specific effects of AA supply, with sufficient duration of intake, adequate sample sizes, and standardized methodology for outcome measurements need careful consideration. • Dose-response studies for LCPUFA intake during the second 6 months of life should be undertaken. • Simplified measures of dietary supply and of LCPUFA status that permit evaluation of large population groups, including young children, should be developed and evaluated.	
IOM, 2012	• Research needs related to health outcomes and related conditions: - Exploration of the causal role for vitamin D in non-skeletal health outcomes. • Research needs related to adverse effects, toxicity, and safety: - To develop innovative methodologies to provide for identification and assessment of adverse effects of excess calcium and vitamin D. - Elucidate adverse effects of long-term, high-dose calcium and vitamin D.	• Minerals • Vitamins

	- Further explore the nature of vitamin D toxicity. • Research related to dose-response relationships: - Conduct studies to identify specific health outcomes in relation to graded and fully measured intakes of calcium and vitamin D. - Clarify the influence of age, body weight, and body composition on serum 25OHD levels in response to intake/exposure.	
SACN, 2010	• Iron intakes and iron status of infants aged up to 18 months need to be better characterized. • An improved understanding of the possible adverse effects of iron supplements on iron-replete children is required. • Further randomized controlled trials with adequate power and sufficient duration are required to examine the effect of iron supplementation on mental development in children under 3 years of age with iron deficiency anemia.	• Minerals
WHO, 2012	• There is a need for high-quality randomized control trials to verify the effects of potassium intake on blood pressure and potential adverse effects in children.	• Minerals
WHO, 2012a	• Further high-quality RCTs with multiple intervention arms directly testing the effect of multiple levels of sodium on health outcomes are warranted to strengthen the evidence base for the target	• Minerals

	sodium intake level.	
WHO, 2011a	• Limited evidence: - Co-interventions that may interact with vitamin A, for example other nutrients and vaccines. - Comparative analysis of the different delivery mechanisms of vitamin A. - Effect of different doses of vitamin A on the critical outcomes of morbidity and mortality, and stratification of the data by sex, length of follow-up, vaccination status, and subsequent vitamin A supplementation. - Identification of field-friendly clinical and biochemical indicators of vitamin A status and vitamin A stores.	• Vitamins
WHO, 2011b	• Further research is needed on the effects of neonatal vitamin A supplementation on infant morbidity and mortality in the first half of infancy in different settings. • Efforts should be made to stratify the effect of supplementation by age at which vitamin A is administered after birth, prematurity and intrauterine growth retardation. • Focus should be placed on populations with endemic maternal vitamin A deficiency and high infant mortality.	• Vitamins

	• Possible interactions with vaccination status and sex also need to be tested. • Studies should be conducted to elucidate the biological mechanisms that may underlie the effects of vitamin A supplements on organ maturation and immune function in human infants. • Additional research is needed on the development of better indicators of vitamin A status in neonates.	
Thomas et al., 2010	• Long-term health benefits of probiotics in the prevention of cancer, allergy, or other diseases or for providing sustained beneficial results on the developing immune system beyond early infancy remain to be proven. • Direct comparison of the health benefits of feeding human milk versus infant formula supplemented with probiotics is needed. Establishing the clinical applications for probiotics (i.e., optimal duration of administration, preferred dose, species) is also needed. • The long-term impact on the gut microflora in children is unknown. • There is a lack of evidence demonstrating the clinical efficacy of oligosaccharides as prebiotics added to infant formula. • Cost/benefit studies are necessary to support infant formula supplementation.	• Probiotics
CPS, 2012	• There needs to be an evaluation of which strains and doses of probiotics should be used for specific	• Probiotics

	conditions.	
ESPGHAN, 2011b	• Randomized controlled trials with validated clinical outcome measures with relevant in-and exclusion criteria and adequate sample sizes are needed. • Independent trials not funded by companies are needed. • There is a lack of data on the long-term effects of the administration of pre- or probiotic-supplemented formula.	• Probiotics

CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrtition; LCPUFA, long-chain polyunsaturated fatty acids

Figure 1. Flow diagram of data selection and identification process