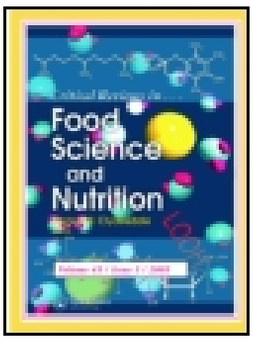

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Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

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To cite this article: Marita de Waard, Brigitte Brands, Stefanie M.P. Kouwenhoven, Joaquim Calvo Lerma, Paula Crespo-Escobar, Berthold Koletzko , Bartlomiej M. Zalewski & Johannes B. van Goudoever (2016): Optimal Nutrition In Lactating Women And Its Effect On Later Health Of Offspring: A Systematic Review Of Current Evidence And Recommendations (Early Nutrition Project), Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2016.1158149

To link to this article: http://dx.doi.org/10.1080/10408398.2016.1158149

Accepted author version posted online: 29 Apr 2016.

Optimal Nutrition In Lactating Women And Its Effect On Later Health Of Offspring: A Systematic Review Of Current Evidence And Recommendations (Early Nutrition Project)

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ABSTRACT

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

Objective To summarize current evidence and standards, recommendations, guidelines, and regulations on nutrition or supplements in lactating women with emphasis placed on long-term

health effects in offspring, including cardiovascular disease, hypertension, overweight/obesity, metabolic syndrome, diabetes, or glucose intolerance.

Methods Medline, Embase, selected databases and websites were searched for documents published between 2010 and 2015.

Results Thirteen documents met the inclusion criteria. Effects of maternal long-chain polyunsaturated fatty acid (LC-PUFA) supplementation on overweight/obesity or hypertension in offspring were assessed in 10 studies. One study described the effect of maternal vitamin D supplementation on overweight/obesity, and the remaining 2 studies assessed the effects of maternal probiotic/synbiotic supplementation during lactation on overweight/obesity or metabolic syndrome in their infants. Forty-one documents contained dietary recommendations on various macro- and micronutrients for lactating women, but without consideration of our long-term health outcomes in infants.

Conclusion Literature on nutrition of lactating women and its effect on their infants' later health with respect to metabolic programming outcomes appeared to be scarce, and focused mostly on supplementation of LC-PUFA's. No recent guidelines or recommendations were available, highlighting the significant research gaps regarding this topic.

Key words

infant, metabolic programming, LC-PUFA, probiotics, Vitamin D

INTRODUCTION

Both fetal and early postnatal life are periods of rapid growth and development during which imbalanced nutrition might result in metabolic or body composition alterations (Gluckman and Hanson 2008). Emerging evidence specifically suggests that increased risk of overweight or obesity later in life is programmed by nutrition during early life (Barker 2004, Gluckman and Hanson 2008, McMillen and Robinson 2005). This relation is thought to be multifactorial and is likely to be U-shaped, with increased risks of adverse health outcomes both for early life undernutrition as well as overnutrition (Gluckman and Hanson 2008). Obesity in children is associated with adolescent and adult onset of non-communicable diseases, such as type 2 diabetes mellitus, cardiovascular disease and hypertension (Agostoni et al. 2013, Barouki et al. 2012).

Given the well-known short- and long-term advantages of breastfeeding for infant and maternal health (vanRossum et al. 2005, Agostoni et al. 2009), leading health authorities such as the World Health Organization (WHO), the American Academy of Pediatrics (AAP) and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) highly recommend breastfeeding as the preferred source of postnatal nutrition. In the context of the fetal-infant programming hypothesis, maternal diet during lactation is thought to contribute to desirable long-term health advantages in children (Luoto et al. 2010, Rush 2001)) including the quality of growth in later life.

EarlyNutrition (www.project-earlynutrition.eu) is an international research project, sponsored by the European Union 7th Framework Programme (Koletzko et al. 2014b). The project's objectives include providing evidence of the effects of early nutrition on metabolic programming and their

consequent health impacts. This project brings together an international consortium of 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 primary objective of the current systematic review, prepared as part of the EarlyNutrition project, was to summarize current evidence from systematic reviews and randomized controlled trials (RCTs) and standards, recommendations, guidelines, and regulations on nutrition in lactating women with emphasis on EarlyNutrition project outcomes. These include the effects on later health of the offspring with respect to adiposity overweight or obesity, cardiovascular disease, hypertension, metabolic syndrome, diabetes, or glucose intolerance. The secondary objective was to identify potential research gaps, as this will enable to develop research agendas.

METHODS

Search strategy

Bibliographic databases, i.e Ovid MEDINE, EMBASE (both http://ovid.com), Cochrane Central Register of Controlled Trials (CENTRAL), and several selected guideline databases or websites of relevant professional organizations that may have produced guidelines were searched in May 2015 (Table 1). In addition, references were obtained by consultation of experts in the field (partners of the EarlyNutrition project). Searches in EMBASE and MEDLINE combined groups of key-words related to our target population, different nutrition components, and the type of preferred documents or study design. The detailed search strategy is provided in Table 2. All other databases, if possible, were searched with a combination of the phrases (infant* or child*)

AND (lactat* OR breastfe* OR 'breast milk') AND (nutrition OR diet). Alternatively, they were simply hand searched.

Searches were limited to human studies published in the last 5 years (2010 and onwards), and restricted to English-language publications.

Selection of Documents

Studies and documents were eligible for inclusion if they were relating to diet and nutrition for lactating women. In addition the documents had to consider the effect of this dietary exposure/intervention on EarlyNutrition health outcomes in the offspring, i.e. adiposity, overweight or obesity, cardiovascular disease, hypertension, metabolic syndrome, diabetes, or glucose intolerance.

We excluded documents focusing exclusively on prevention or treatment of a particular disease, such as allergic diseases or iron deficiency anaemia that were not related to the outcomes mentioned above, or that focused on the period of pregnancy only. In addition, scientific documents other than randomized controlled trials, systematic reviews and meta-analysis, and documents dedicated to a local community, without national or international outreach were excluded.

Two authors (MDW and either SK, PCE or JCL) searched the provided sources and screened titles, abstracts and then full-text reports for inclusion independently. The total list of titles was additionally screened by BB. Any discrepancies were resolved through discussion or by consultation with an expert in the field.

Data extraction process

For each eligible study MDW, SK, PCE, and JCL independently extracted the following data: general information (title, author, year of publication, type of document: scientific trial or guideline, recommendation or consensus statement), document characteristics (scientific trial: design, participants characteristics, intervention and control regimens), the impact on defined health outcomes, and authors' suggestions for further research/identified research gaps. Other documents: report type, target population, brief recommendation, the impact on defined health outcomes, the level of evidence (if stated by the authors), and authors' suggestions for further research/identified research gaps. Inconsistencies were checked and resolved through discussion. We did not perform any formal methodological assessment of the included documents' 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

Research gaps, associated with EarlyNutrition outcomes, were extracted from the identified documents if recognized by the authors of the documents.

RESULTS

Selection of Documents

Figure 1 shows a detailed description of the study selection process. The search strategy yielded 4218 documents, 3902 of which were excluded based on title or abstract. Full text evaluation of the remaining 316 records identified 13 documents that met our selection criteria. None of these were guidelines or clinical protocols.

The effect of maternal fatty acid supplementation was assessed in 10 of the included studies, 1 study described the effect of Vitamin D supplementation and the remaining 2 assessed the effects

of maternal probiotics/synbiotic supplementation during lactation. An outline of all included studies is provided in Table 3.

Forty-one of the excluded documents did contain dietary recommendations on various macro- and micronutrients for lactating women (Table 4), but without consideration of our EarlyNutrition outcomes.

Long-chain polyunsaturated fatty acid supplementation during lactation

Seven of the included publications on maternal long-chain polyunsaturated fatty acid (LC-PUFA) supplementation were systematic reviews (Stratakis et al. 2014, Rodriguez et al. 2012, Muhlhausler et al. 2010, Martinez-Victoria and Yago 2012, Koletzko et al. 2014b, Delgado-Noguera et al. 2015, Campoy et al. 2012), one of which a Cochrane review (Delgado-Noguera et al. 2015). The remaining 3 documents were original reports of randomized controlled trials (RCTs) (Jensen et al. 2010, Hauner et al. 2012, Bergmann et al. 2012) (Table 3).

The 7 systematic reviews enclosed a total of 10 publications (describing outcomes of 5 randomized trials), including the 3 RCTs we identified. The remaining 7 publications were published before the year 2010, and were therefore not individually identified by our search (Ulbak et al. 2004, Lucia Bergmann et al. 2007, Lauritzen et al. 2005, Jensen et al. 2005, Helland et al. 2008, Helland et al. 2001, Asserhoj et al. 2009). Their results were however included in the current review, since the previous reviews were based upon them (Table 4).

The (updated) Cochrane review was the most recently published document and included all 10 publications. The remaining systematic reviews included part, but not all, of the publications (Table 3).

The effects of LC-PUFA supplementation exclusively during *lactation* was described in 1 systematic review, whereas 2 others additionally included supplementation during both *pregnancy and lactation*. The remaining 4 reviews also included supplementation only during *pregnancy*. Since this subject did not fall within the scope of the current review, we did not recite results exclusively on this topic.

Doses of n-3 LCPUFA in the described intervention groups ranged from 200 mg docosahexaenoic acid (DHA) to 1183 mg DHA plus 803 mg eicosapentaenoic acid (EPA) (with a total of 2494 mg n-3 LC-PUFA), and were derived from fish oil or algal oils.

Intervention periods extended from 15, 18 or 21 weeks of pregnancy to 3 or 4 months after delivery or exclusively during the first 4 months postpartum.

The EarlyNutrition outcome 'overweight/obesity' was assessed in 9 publications, at various time-points, and with various parameters (i.e. weight, body mass index, and fat mass and fat distribution) (Lucia Bergmann et al. 2007, Lauritzen et al. 2005, Jensen et al. 2005, Jensen et al. 2010, Helland et al. 2008, Helland et al. 2001, Hauner et al. 2012, Bergmann et al. 2012, Asserhoj et al. 2009).

Table 5 summarizes the results, which were categorized into short-term (up to 12 months), medium-term (up to 24 months), and long-term (beyond 24 months) outcomes according to Delgado et al. (Delgado-Noguera et al. 2015).

All included reviews came to the same conclusion that evidence on the potential relationship between maternal n-3 LC-PUFA intake and infant growth or later body composition was inconclusive. Supplementation with LC-PUFA did not seem to exert a clear and consistent short-

or long-term benefit in offspring, and any transient early differences disappeared in subsequent assessments.

The EarlyNutrition outcome 'hypertension' was assessed in 2 of the publications based on the same RCT (Ulbak et al. 2004, Asserhoj et al. 2009). At 2.5 years of age no difference in either systolic or diastolic blood pressure (SBP and DBP) between groups was observed. At 7 years of age, children in the LC-PUFA supplemented group had a higher unadjusted mean SBP and mean arterial pressure (MAP). After adjustment for covariates SBP did not differ between the randomized groups anymore. Due to an interaction between intervention and sex ($p = 0.027$ for DBP and $p = 0.026$ for MAP), adjusted ANOVA was performed separately for the 2 sexes. Among boys, both DBP and MAP differed between the randomized groups, but blood pressure of girls did not.

Vitamin D supplementation during lactation

The one publication on vitamin D intake during lactation referred to the EarlyNutrition outcome overweight/obesity, and was a prospective, double blinded, randomized controlled trial of vitamin D supplementation during lactation in both mother and infant (Czech-Kowalska et al. 2014).

Examined outcomes in the infants were weight, length, head circumference, and body composition (fat mass) by dual-energy X-ray absorptiometry (DXA) measurements at three time points: 3 weeks after delivery (baseline visit), and 3 and 6 months after delivery. The maternal intervention group received 1200 IU/d of cholecalciferol, the control group 400 IU/d. All breastfed infants received 400 IU/d. No significant differences in body composition and bone mass as examined by DXA were found between the intervention groups at any time point.

However, serum hydroxy-vitamin D status (25(OH)D) was significantly higher in the 1200 IU/d group although the recommended level (>20ng/ml by the Institute of Medicine (IOM) or >30ng/ml (Pludowski et al. 2013a, Holick et al. 2011, Pludowski et al. 2013b) was still not reached in many women. This might have been due to the low baseline levels at study entry (65% of postpartum vitamin D deficiency) which highly depends on the maternal diet before birth and to sun exposure.

Probiotic and synbiotic supplementation during lactation

Two publications of RCTs referring to probiotic or synbiotic (both pre-and probiotic) supplementation in lactating mothers, assessing the EarlyNutrition outcomes overweight/obesity and metabolic syndrome were identified. (Aaltonen et al. 2011, Ostadrahimi et al. 2013). In the first RCT, by Aaltonen et al. 256 pregnant women in Finland were randomized to receive dietary counselling + a probiotic supplement, dietary counselling + placebo, or no counselling + placebo, starting in the first trimester until six months after delivery. Anthropometrics of the offspring were measured at three study visits (1^{st} trimester, 3^{rd} trimester, and 6 months post-delivery). In addition, infants' breastfeeding status was recorded and their metabolic status was evaluated, by serum 32-33 split proinsulin. This is a novel marker of adverse metabolic status in infancy, and has previously been shown to be a well-characterized predictor for insulin resistance in adults and older children (Mykkanen et al. 1997). The authors found that the infants' risk of high 32-33 split proinsulin concentration was significantly lower in the dietary counselling + probiotics and dietary counselling + placebo groups, compared to the control group. In a multivariate analysis, the independent effect of dietary counselling on the infants' 32-33 split proinsulin was still statistically significant (with breastfeeding and mother's glucose level at 6

months, and weight gain during pregnancy). However, there was no effect of the probiotic supplementation in this population.

The second trial, by Ostradahimi et al. in 2013, was conducted in lactating mothers and their exclusively breastfed infants in Iran. The authors examined the effect of a synbiotic supplement on infant weight and growth (synbiotic: n = 40, placebo, n = 40). They found that the administration of synbiotics may prevent weight loss in undernourished lactating mothers, enhance breastfeeding duration and infant weight gain.

Research gaps

Research gaps as identified and described by the authors of the 13 included studies were summarized in Table 6. All included systematic reviews on maternal LC-PUFA supplementation pointed out that there was a wide variation in interventions, outcome parameters and follow-up periods between trials and that most trials were prone to methodological limitations. In addition, identified research gaps comprised a lack of control for nutritional status and intakes at baseline, as well as for genetic variation. The latter was based on the identification of polymorphisms in the fatty acid desaturase (FADS) gene cluster (Glaser et al. 2011, Lattka et al. 2011). This gene plays a role in the conversion of n-3 LC-PUFA's from their precursors, and it was demonstrated that pregnant and lactating women with the less common genotypes of the FADS gene cluster had very low conversion rates (Koletzko et al. 2011, Lattka et al. 2011, Steer et al. 2013).

For vitamin D supplementation, the authors stated that taking into account previous studies, vitamin D supplementation seems to be a more effective source for supplementation than additional input from diet and endogenous skin synthesis in many contemporary industrialized

populations with changing lifestyles (sun exposure, obesity, unhealthy diet). Yet, they feel that more studies are needed in various settings, specifically addressing infants' long-term outcomes.

The identified research gap for studies on pro- and synbiotic supplementation was the need for targeted studies to evaluate the independent effect of synbiotic supplementation in lactating mothers on infants' health outcomes.

DISCUSSION

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 assessing the effect of nutrition of lactating women on their infants' later health with respect to adiposity, overweight or obesity, cardiovascular disease, hypertension, metabolic syndrome, diabetes, or glucose intolerance. Literature on this topic appeared to be scarce, and focused mostly on the supplementation of LC-PUFA's. In the past 5 years, no guidelines or recommendations on nutrition in breast-feeding women relating to our defined effects on their offsprings' health were published.

The lack of literature and guidelines was unsuspected, since the programming hypothesis of early life nutrition now is a pertinent topic. The hypothesis proposes that overweight or obesity, impaired glucose metabolism, and heightened blood pressure are modulated by environmental cues that originate in developmental plasticity, including nutritional aspects (Barker 2004).

In both developed and less developed countries, excess body weight is now a major health problem; more than 20% of children and adolescents in Europe and more than 30% in the US suffer from overweight or obesity (www.IASO.org). Becoming obese earlier in life clearly amplifies certain health risks such as type 2 diabetes. Based on the fetal-infant programming

hypothesis it has been suggested that attempts to prevent obesity should start during early life. Alteration of early exposure to certain nutrients via maternal diet during lactation is such an attempt. However, our current review showed that (human) evidence for the effectiveness of this is so far scarce and limited to interventions with LC-PUFAs, vitamin D and probiotics/synbiotics.

Acquisition of fat cells early in life appears to be an irreversible process, and early exposure to n-3 LC-PUFA's is suggested to have the potential to limit adipose tissue deposition, mainly by limiting the production of prostacyclin which has been shown to enhance adipogenesis. A deficiency in vitamin D during breastfeeding has been shown to be associated with a range of negative health outcomes in mother and child, such as cardiovascular disease, hypertension and diabetes (Pludowski et al. 2013a). Finally, research in animals and humans has shown that probiotics have an effect on the host energy metabolism by altering the gut microbiota. The combination of probiotics and prebiotics, referred to as synbiotics, may affect the host by improving the survival and the implementation of live bacterial strains in the gastrointestinal tract, thus exerting potentiated positive health effects. Our results showed that there is little evidence to support a favorable programming effect by maternal n-3 LC-PUFA or vitamin D supplementation during lactation. One small trial suggested that there might be a possible positive effect of maternal probiotic/synbiotic supplementation on infants' weight gain and body composition. Yet, much more evidence is needed to support these findings and to formulate evidence-based recommendations.

A major part of the documents excluded from this review focused on nutrition in lactating women, and some of them did include recommendations (Table 4). However, most of these

recommended intakes were extrapolated from known losses of nutrients in milk, sometimes with adjustment for bioavailability, and not on possible health effects for the infants. Studies analysing those losses also emerged from our literature search. Although these studies did not fall within the scope of our review, they can be considered crucial early stages for the documents that we were searching for, since effects of nutrients on health of offspring can only be expected if certain levels in breast-milk will be reached. Research on the extent to which the nutrient composition of human milk can be affected by maternal status and intake is on the other hand scarce (Allen). In the past, nutrients have been categorized into 2 groups during lactation. Poor maternal status of group I nutrients (thiamin, riboflavin, vitamin B-6, vitamin B-12, choline, retinol, vitamin A, vitamin D, selenium and Iodine) results in low concentrations of these nutrients in breast milk whereby the infant becomes depleted, whereas group II nutrients (folate, calcium, Iron, copper, and zinc) in breast milk are relatively unaffected by maternal intake or status; the mother gradually becomes more depleted when intake is less than the amount secreted in milk, but milk concentrations are maintained (Allen). Future research focussing on supplementation of group I nutrients in lactating women is therefore to be expected to show the clearest results on infants' health.

The major strength of the current review is the extensive search strategy. Limitations were the restriction to English-language publications leading to the possibility that eligible documents in other languages may have been omitted, and the restriction on year of publication. To ensure that we included the latest and most up-to-date documents we only considered documents published from 2010 onwards, in order to be consistent with other systematic reviews performed as part of the EarlyNutrition project. It is therefore possible that we have not included some potentially

relevant documents. On the other hand, as systematic reviews were included, with studies originating more than 5 years ago, we are quite confident that the important studies are included. Another limitation is that we did not set out to critically appraise the documents that we identified, in terms of their quality, nor did we directly assess any of the information that the documents and conclusions were based upon.

CONCLUSIONS

This systematic review of current literature and recommendations on nutrition of lactating women and its effects on later health outcomes in their offspring showed that current evidence is scarce and many aspects of nutrition need further elucidation. This review can form a foundation for further research based on gaps provided by the authors of included documents and identified during the process of this review.

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].

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Table 1: Sources searched

Cochrane Database of Systematic Reviews (CDSR) http://www.thecochranelibrary.com/
Database of Abstracts of Reviews of Effects (DARE) http://www.crd.york.ac.uk/crdweb/
PROSPERO: international prospective register of systematic reviews http://144.32.150.25/PROSPERO/
Health Technology Assessment (HTA) Database http://www.crd.york.ac.uk/crdweb/ [or as part of The Cochrane Library]
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
Clinical Evidence http://clinicalevidence.bmj.com/ceweb/conditions/index.jsp
NHS Evidence http://www.evidence.nhs.uk/default.aspx
NHS Clinical Knowledge Summaries (formerly PRODIGY)http://www.cks.nhs.uk/home
Health Systems Evidence: a continuously updated repository of syntheses of research evidence about governance, financial and delivery arrangements within health systems, and about implementation strategies that can support change in health systems 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, http://www.aap.org/ • World Health Organization, http://www.who.int/publications/guidelines/en/index.html • Institute of Medicine, http://www.iom.edu/ • Scientific Committee on Nutrition, http://www.sacn.gov.uk/ • EFSA, http://www.efsa.europa.eu/en/publications.htm • Guidelines International Network, http://www.g-i-n.net • Deutsche Adipositas Gesellschaft, http://www.adipositas-gesellschaft.de/ • Association for the Study of Obesity, http://www.aso.org.uk/ • World Obesity Federation, http://www.worldobesity.org/ • European Association for the Study of Obesity, http://easo.org/ • European Association for the Study of Diabetes, http://www.easd.org/

- Deutsche Diabetes Gesellschaft, www.deutsche-diabetes-gesellschaft.de
- Verband der Diabetes-Beratungs- und Schulungsberufe in Deutschland e.V., https://www.vdbd.de/index.php
- International Diabetes Federation, http://www.idf.org/
- Deutsche Gesellschaft für Endokrinologie, http://www.endokrinologie.net/
- Schweizerische Gesellschaft für Endokrinologie und Diabetologie, http://www.asemo.ch/
- Society for Endocrinology, http://www.endocrinology.org/index.aspx
- Canadian Society of Endocrinology and Metabolism, http://www.endo-metab.ca/
- European Society of Endocrinology, http://www.ese-hormones.org/
- Endocrine Society, http://www.endocrine.org/
- Deutsche Gesellschaft für Epidemiologie, http://www.dgepi.de/
- International Society for Developmental Originas of Health and Disease, http://www.mrc-leu.soton.ac.uk/dohad/index.asp
- International Epidemiological Association, http://ieaweb.org/
- International Genetic Epidemiology Society, http://www.geneticepi.org/

- Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten, http://www.dgvs.de/
- Österreichische Gesellschaft für Gastroenterologie und Hepatologie, http://www.oeggh.at/
- Schweizerische Gesellschaft für Gastroenterologie, http://www.sggssg.ch/home.html
- United European Gastroenterology, https://www.ueg.eu/
- World Gastroenterology Organisation, http://www.worldgastroenterology.org/
- Bundesverband Deutscher Ernährungsmediziner e.V., http://bdem.de/
- Deutsche Gesellschaft für Ernährung, https://www.dge.de/
- Deutsche Gesellschaft für Ernährungsmedizin e. V., http://dgem.de/
- Berufsverband der Oecotrophologie e.V., http://www.vdoe.de/
- Verband der Diätassistenten e.V., http://www.vdd.de/
- American Society for Nutrition, http://www.nutrition.org/
- Parenteral and Enteral Nutrition Society of Asia, http://www.pensa-online.org/index.php
- European Society for Clinical Nutrition and Metabolism, http://www.espen.org/

- European Federation of the Associations of Dietitians, http://www.efad.org
- International Union of Nutritional Sciences, http://www.iuns.org/
- Berufsverband Kinder- und Jugendärzte e.V., http://www.bvkj.de/
- Deutsche Gesellschaft für Kinder- und Jugendmedizin e.V., http://www.dgkj.de/
- Gesellschaft für Pädiatrische Gastroenterologie und Ernährung e.V., http://www.gpge.de/index.html
- Österreichische Gesellschaft für Kinder- und Jugendheilkunde, http://www.docs4you.at/
- Swiss Society of Neonatology, http://www.neonet.ch/en/about-us/aims/
- Pediatric Society in Bosnia and Herzegovina, http://www.upubih.org/
- Paediatric Research Society, http://www.prs.nhs.uk
- Paediatric Society New Zealand, http://www.paediatrics.org.nz/events.asp?pageID = 2145870907
- American Pediatric Society together with the Society for Pediatric Research, https://www.aps-spr.org/home.asp
- Canadian Paediatric Society, http://www.cps.ca/en/

- Canadian Neonatal Network, http://www.canadianneonatalnetwork.org/portal/
- Asia Pacific Paediatric Endocrine Society, http://www.appes.org/AboutUs.aspx
- European Society for Paediatric Research, http://www.espr.info/
- European Paediatric Association, http://www.epa-unepsa.org/
- European Society for Neonatology, http://esn.espr.info/
- European Foundation for the Care of Newborn Infants, http://www.efcni.org/
- European Society for Paediatric Endocrinology, http://www.eurospe.org/index.aspx
- Union of European Neonatal & Perinatal Societies, http://www.uenps.com/
- European Academy of Paediatrics, http://www.eapaediatrics.eu/index.ehtml
- Vermont Oxford Network, https://public.vtoxford.org/
- International Confederation of Midwives, http://www.internationalmidwives.org/

Table 2: Medline and Embase search strategy

1.	LACTATION/
2.	(LACTATION or LACTAT$).ti,ab.
3.	BREAST FEEDING/
4.	(BREAST-FE$ or BREASTFE$).ti,ab.
5.	(BREASTFEED$ or BREAST-FEED$).ti,ab.
6.	(BREAST-MILK or BREASTMILK).ti,ab.
7.	HUMAN MILK/
8.	HUMAN MILK.ti,ab.
9.	(LACTATING MOTHER or LACTATING WOMAN or LACTATING WOMEN).ti,ab.
10.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11.	(DIET$ or FOOD$ or EAT 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 FOOD SAFETY or SUPPLEMENT$ or FISH OIL or PROBIOTIC$ or PREBIOTICS$ or FOOD GROUP$ or DIET$ QUALITY or DIET$ PATTERN$ or FOLIC ACID or MAGNESIUM or SELENIUM or ZINC or PYRIDOXINE or RIBOFLAVIN or NICOTINIC ACID or DIETARY SALT or ALCOHOLIC DRINK$ or ALCOHOL).ti.
12.	(DIET$ or FOOD$ or EAT 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 FOOD

	SAFETY or SUPPLEMENT$ or FISH OIL or PROBIOTIC$ or PREBIOTICS$ or FOOD GROUP$ or DIET$ QUALITY or DIET$ PATTERN$ or FOLIC ACID or MAGNESIUM or SELENIUM or ZINC or PYRIDOXINE or RIBOFLAVIN or NICOTINIC ACID or DIETARY SALT or ALCOHOLIC DRINK$ or ALCOHOL).ab.
13.	DIET/ or exp FOOD/ or NUTRITION/ or exp FRUIT/ or exp VEGETABLES/ or DIETARY IRON/ or DIETARY CALCIUM/ or exp DIETARY FATS/ or exp DIETARY PROTEINS/ or DIETARY CARBOHYDRATES/ or exp VITAMINS/ or exp RIBOFLAVIN/ or exp NICOTINIC ACIDS/ or PYRIDOXINE/ or ZINC/ or FOLIC ACID/ or MAGNESIUM/ or SELENIUM/ or SODIUM, DIETARY/ or exp ENERGY INTAKE/
14.	11 or 12 or 13
15.	10 and 14
16.	exp ANIMALS/ not HUMANS.sh.
17.	15 not 16
18.	exp ASIA/ or exp AFRICA/ or exp SOUTH AMERICA/ or exp DEVELOPING COUNTRIES/
19.	17 not 18
20.	exp PRACTICE GUIDELINES/
21.	HEALTH PLANNING GUIDELINES/
22.	GUIDELINE$.ti.
23.	(PRACTICE adj3 PARAMETER$).ti,ab.

24.	CLINICAL PROTOCOLS/
25.	GUIDANCE.ti,ab.
26.	CARE PATHWAY$.ti,ab.
27.	CRITICAL PATHWAY/
28.	(CLINICAL adj3 PATHWAY$).ti,ab.
29.	CONSENSUS DEVELOPMENT CONFERENCE.pt.
30.	CONSENSUS DEVELOPMENT CONFERENCE NIH.pt.
31.	(((comprehensive* or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or ((cochrane adj3 trial*) or "web of science").ab. or "cochrane database of systematic reviews."jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt.
32.	("clinical trial" or "clinical trial, phase i" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or double-blind method/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab.
33.	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

34.	19 and 33
35.	limit 34 to yr = “2010 -Current”

Table 3: Summary description of documents included

Reference	Included in	Study Design	Year	Moment of Intervention	Early Nutrition Infant outcome
VITAMIN D					
Czech-Kowalska et al. (Czech-Kowalska et al. 2014)	-	RCT	2014	- Lactation (3 wks pp)	Overweight/obesity
SYNBIOTICS/PROBIOTICS					
Ostadrahimi et al. (Ostadrahimi et al. 2013)	-	RCT	2013	- Lactation	Overweight/obesity Metabolic syndrome
Aaltonen et al. (Aaltonen et al. 2011)	-	RCT	2011	- Pregnancy (1^{st} and 3^{rd} trimester) - Lactation (6 mo pp)	Overweight/obesity
LC-PUFA					
Campoy et al. (Campoy et	-	Systemati	201	-	Overweight/obesit

al. 2012)		c review	2	Pregnancy - Lactation - Both	y
Koletzko et al. (Koletzko et al. 2014a)	-	Systematic review	2014	- Pregnancy - Lactation - Both	Overweight/obesity Hypertension
Martínez-Victoria et al. (Martinez-Victoria and Yago 2012)	-	Systematic review	2012	- Pregnancy - Lactation - Both	Overweight/obesity
Stratakis et al. (Stratakis et al. 2014)	-	Systematic review	2014	- Pregnancy - Lactation - Both	Overweight/obesity
Muhlhausler et al.(Muhlhausler et al. 2010)	-	Systematic review	2010	- Lactation - Both	Overweight/obesity
Rodriguez et al. (Rodriguez et al. 2012)	-	Systematic review	2012	- Both pregnancy and	Overweight/obesity

				lactation	
				- Lactation only	
Delgado et al. (Delgado-Noguera et al. 2015)	-	Cochrane review	2015	- Both pregnancy and lactation	Overweight/obesity
				- Lactation only	
RCTs included in systematic reviews on LC-PUFAs, and describing (one of) our outcomes: published 2010-onwards					
Hauner et al.(Hauner et al. 2012)	Delgado Koletzko Rodriguez	RCT	2012	- Both pregnancy and lactation	Overweight/obesity
				(15 w PCA--4 mo pp)	

Bergmann RL et al.(Bergmann et al. 2012)	Delgado Stratakis	RCT	2012	- Pregnancy (21 w--37 wks PCA) - Lactation (delivery--3 mo pp)	Overweight/obesity
Jensen et al. (Jensen et al. 2010)	Campoy Delgado	RCT	2010	- Lactation (5 days--4 mo pp)	Overweight/obesity
RCTs included in systematic reviews on LC-PUFAs, and describing (one of) our outcomes: published before 2010					
Asserhoj et al. (Asserhoj et al. 2009)	Delgad Muhlhauser Koletzko Rodriguez Stratakis	RCT	2009	- Lactation (2 w--4 mo pp)	Overweight/obesity Hypertension
Helland et al. (Helland et al. 2008)	Campoy Delgado Koletzko Muhlhause	RCT	2008	- Both pregnancy and lactation	Overweight/obesity

	r Rodriguez Stratakis			(18 w PCA--3 mo pp)	
Lucia Bergmann et al. (Lucia Bergmann et al. 2007)	Campoy Delgado Martínez-Victoria Muhlhauser Rodriguez Stratakis	RCT	2007	- Pregnancy (21 w--37 w PCA) - Lactation (after delivery 3 mo pp)	Overweight/obesity
Lauritzen et al. (Lauritzen et al. 2005)	Delgado Martínez-Victoria Muhlhauser Rodriguez Stratakis	RCT	2005	- Lactation (2 w--4 mo pp)	Overweight/obesity
Jensen et al. (Jensen et al. 2005)	Campoy Delgado	RCT	2005	- Lactation (5 days--4 mo pp)	Overweight/obesity

Ulbak et al. (Ulbak et al. 2004)	Delgado	RCT	2004	- Lactation (2 w--4 mo pp)	Hypertension
Helland et al.(Helland et al. 2001)	Campoy Delgado Martínez-Victoria	RCT	2001	- Both pregnancy and lactation (18 w PCA--3 mo pp)	Overweight/obesity

LC-PUFA; long chain- polyunsaturated fatty acid. PCA; post-conceptual age. PP; postpartum. DHA; docohexaenoic acid. EPA; eicosapentaenoic acid. GA; Gestational age. FOS; Fructo-oligosaccharide. W; weeks. Mo; months. y; years. BMI; body mass index. HC; head circumference.

Table 4. Dietary recommendations in excluded documents

REFERENCE	RECOMMENDATION
MACRONUTRIENTS & OVERALL ENERGY INTAKE	
EFSA 2013 Scientific Opinion on Dietary Reference Values for energy	For exclusive breastfeeding during the first six months of life, the mean energy expenditure of lactation over this period is 2.8 MJ/day (670 kcal/day) based on a mean milk production of 807 g/day, an energy density of milk of 2.8 kJ/g (0.67 kcal/g), and an energetic efficiency of 80%. Energy mobilization from tissues in the order of 0.72 MJ/day (170 kcal/day) may contribute to this energy expenditure and reduce the additional energy requirement during lactation to *2.1 MJ/day (500 kcal/day)* over pre-pregnancy requirements.
EFSA 2010 Scientific Opinion on Dietary Reference Values for water	Adequate intake of water for females is *2.0 L/day* (P95: 3.1 L). Adequate intake for lactating women is approximately *700 mL/day higher.*
Australian dietary guidelines 2013	Minimum recommended intake for lactating women are *> 7 serves/day of vegetables 2 serves/day of fruit 8½ serves/day of grain/cereal (2 slices of bread = 2 serves.) 2½ serves/day for milk, yoghurt, cheese and/or alternatives 2½ serves/day for lean meats and poultry, fish, eggs, tofu, nuts and seeds, and legumes/beans* For women who are lactating, not drinking alcohol is the safest option.
WHO 2013	Women in the postnatal period need to maintain a balanced diet. Iron

Counselling for maternal and newborn health care A handbook for building skills	and folic acid supplementation should also continue for 3 months after birth. Women who are breastfeeding require additional food and should drink sufficient clean water.
Australia and New Zealand, Early Life Nutrition, Working Party 2014 Nurturing future health through nutrition	Typically, a breastfeeding woman needs an additional *2,000--2,100kj* per day over the recommended daily intake for women. The energy intake of a breastfeeding woman would be *at least 20% fat* -- any less may affect the fat content of your milk. Ensure an adequate intake of iodine (*150mg daily*) and other important vitamins and minerals. In case of a vegan, vegetarian, or other restrictive diet, there may be a greater risk for nutrient deficiencies. Consideration of seeing a dietitian to ensure the diet is nutritionally balanced to meet the needs of breastfeeding is needed.
EFSA 2012 Scientific Opinion on Dietary Reference Values for protein	For lactation a protein intake of *19 g/day* during the first six months, and *13 g/day* after six months is recommended.
EFSA 2012 Scientific Opinion on the Tolerable Upper Intake Level of EPA, DHA and DPA1	Available data are insufficient to establish an upper limit for n-3 LC-PUFA (individually or combined) for any population group.

EFSA 2010 Scientific Opinion on Dietary Reference Values for fats	The Panel proposes to set an adequate intake of 250 mg for eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) for adults based on cardiovascular considerations. To this intake *100 to 200 mg* of preformed DHA should be added during lactation to compensate for oxidative losses of maternal dietary DHA and accumulation of DHA in body fat of the infant.
Dietary Guidelines for Americans 2010	For lactating women consuming *8-12 ounces/week* of seafood from a variety of seafood types is associated with improved infant health outcomes, such as visual and cognitive development. Lactating women should limit white (albacore) tuna to *6 ounces/week* and should not eat tilefish, shark, swordfish, and king mackerel, due to their high methyl mercury content. Lactating women should be very cautious about drinking alcohol, if they choose to drink at all.
NGC 2010 NGC-8567	Women who are breastfeeding should consume *8 to 12 ounces of seafood* per week from a variety of seafood types. Due to their high methyl mercury content, lactating women should limit white (albacore) tuna to *6 ounces per week* and should not eat the following four types of fish: tilefish, shark, swordfish, and king mackerel. They should maintain appropriate calorie balance to maintain weight during breastfeeding.
MICRONUTRIENTS: GENERAL ADVICE	
SACN 2011 Early Life	There are increased requirements for a number of nutrients for

Nutrition Report	lactation. These include referent nutrient intakes set for the provision of energy (for different stages of lactation), protein, folate, vitamin A, vitamin D, vitamin C, B vitamins (thiamin, riboflavin, niacin, vitamin B12) and also for a number of minerals (calcium, phosphorus, magnesium, zinc, copper and selenium) [Department of Health, 1991]. Current advice is that all of these intakes can be achieved through a varied and balanced diet, apart from vitamin D, which requires a *10 µg daily* supplement for the duration of breastfeeding in order to ensure the requirement is met.
WHO 2013 Essential Nutrition Actions: Improving Maternal, Newborn, Infant and Young Child Health and Nutrition.	Recommended composition of multiple micronutrient supplements for lactating women, designed to provide the daily recommended intake of each nutrient (one RNI): *Vitamin A 800 µg, Vitamin D 5 µg, Vitamin E 15 mg, Vitamin C 55 mg, Thiamine (vitamin B1) 1.4 mg, Riboflavin (vitamin B2) 1.4 mg, Niacin (vitamin B3) 18.0 mg, Vitamin B6 1.9 mg, Vitamin B12 2.6 µg, Folic acid 600 µg, Iron 27.0 mg, Zinc 10 mg, Copper 1.15 mg, Selenium 30 µg, Iodine 250 µg* Lactating women should be given this supplement providing one reference nutrition intake (RNI) of micronutrients daily, whether they receive fortified rations or not. Iron and folic acid supplements, when already provided, should be continued.
CALCIUM	
EFSA 2012 Scientific	The upper limit for calcium for all adults, including lactating women

Opinion on the Tolerable Upper Intake Level of calcium	is *2,500 mg.* This upper limit was based on different long-term intervention studies in which a total daily intake of 2,500 mg of calcium/day from all sources (diet and supplements) was tolerated without adverse effects.
FOLATE	
EFSA 2014 Scientific Opinion on Dietary Reference Values for folate	The Panel notes that the average folate concentration of breast milk is 80 μg/L (about 180 nmol/L) and that this amount is not dependent on dietary folate intake or status of the lactating women. The Panel considers that lactating women have increased folate requirements compared with non-lactating women to compensate for folate losses through their milk. A lactating woman would require 128 μg/day of additional folate to compensate for her losses. A value of 130 μg/day is added to the average requirement for non-lactating women, resulting in an average requirement of *380 μg DFE/day*, with a population reference intake of 500 μg DFE/day.
IODINE	
NHMRC public statement 2010 Iodine Supplementation for Pregnant and Breastfeeding Women	The National Health and Medical Research Council (NHMRC) recommends that all women who are breastfeeding take an iodine supplement of 150 μg each day. Women with pre-existing thyroid conditions should seek advice from their medical practitioner prior to taking a supplement.
WHO 2013 Essential	WHO and UNICEF recommend iodine supplementation (*240 μg/day*

Nutrition Actions: Improving Maternal, Newborn, Infant and Young Child Health and Nutrition.	*or 400mg/year*) for lactating women in countries where less than 20% of households have access to iodized salt, until the salt iodization program is scaled up.
WHO 2014 Fortification of food-grade salt with iodine for the prevention and control of iodine deficiency disorders	It is recommended that lactating women consume *250 µg* of iodine per day.
EFSA 2014 Scientific Opinion on Dietary Reference Values for iodine	Iodine concentrations in breast milk of European women vary widely and large iodine stores exist in conditions of adequate iodine status before lactation. The Panel therefore considered that a full compensation for the iodine secreted in breast milk may not be justified for the derivation of dietary reference values for iodine for lactating women. Therefore, for lactating women the same adequate intake is proposed as for pregnant women, i.e. *200 µg/day*.
VITAMIN A	
Gogia S. et al 2011 (PMID 21975770)	There is no convincing evidence that maternal vitamin A supplementation *(both <200.000IU/day and ≥200.000IU/day)* during lactation results in a reduction in infant mortality or morbidity in

	low and middle income countries.
WHO 2011 Guideline: Vitamin A Supplementation in Postpartum Women	Vitamin A supplementation in postpartum women is not recommended for the prevention of maternal and infant morbidity and mortality.
EFSA 2015 Scientific Opinion on Dietary Reference Values for vitamin A	Vitamin A population reference intakes for women are *650 µg retinol equivalent/day*. For lactation, additional vitamin A requirements of *1300 µg retinol equivalent/day* are recommended, related to transfer of retinol into breast milk.
VITAMIN C	
EFSA 2013 Scientific Opinion on Dietary Reference Values for vitamin C	Lactating women secrete vitamin C via breast milk. Vitamin C concentration in human milk reflects maternal vitamin C intake more than the infants' requirement (WHO/FAO, 2004). The Panel notes that mean vitamin C concentration of human milk from healthy mothers not taking vitamin C supplements is in the range of 35-90 mg/L. For lactating women *60 mg/day* in addition to the population reference intake of *95 mg/day* of non-lactating women are proposed.
VITAMIN D	
EFSA 2012 Scientific Opinion on the Tolerable Upper Intake Level of vitamin D	The upper limit of vitamin D for all adults, including lactating women is *100 µg/day*.

NICE 2014 NICE guidelines [PH56]	Population groups at higher risk of having a low vitamin D status including all breastfeeding women, particularly teenagers and young women, are currently advised to take a supplement that meets 100% of the reference nutrient intake for their age group. This is *10 μg/day (400 IU)* for adults.
NICE public health guidance 11, 2014 Maternal and child nutrition	In 1991, Committee on Medical Aspects of Food and Nutrition Policy set a reference nutrient intake (RNI) of 10 μg of vitamin D per day for all pregnant and breastfeeding women. In 2007, the Scientific Advisory Committee on Nutrition confirmed that these recommendations should remain unchanged.
Public Health England 2014 Vitamin D: for healthcare professionals and the public	Lactating women should take a vitamin D supplement (*10 μg/day*) to ensure they get enough vitamin D.
NGC 2011 NGC-6418	Midwives should offer every woman information and advice on the benefits of taking a vitamin D supplement *(10 μg/day)* while breastfeeding. They should explain that it will increase both the mother's and her baby's vitamin D stores and reduce the baby's risk of developing rickets.
SIGN 2010 Management of obesity	It is recommended that breastfeeding mothers take a supplement containing *10 μg* vitamin D.
IoM 2011 Dietary	There is no evidence that calcium requirements are different for

Reference Intakes for Calcium and Vitamin D	lactating females compared with non-lactating counterparts, since post-lactation maternal bone mineral is restored without consistent evidence that higher calcium intake is required. The estimated average requirement for calcium for non-lactating women and adolescents are applicable, which are *800 mg/day* and *1,100 mg/day* respectively. Increased maternal vitamin D intakes increase maternal serum 25OHD levels, with no effect on the neonatal serum 25OHD levels of breastfed infants unless the maternal intake of vitamin D is extremely high (i.e., 4,000 to 6,400 IU/day). Observational studies report no relationship between maternal serum 25OHD levels and bone mass density. There is no evidence that lactating adolescents require any more vitamin D or higher serum 25OHD levels than non-lactating adolescents. The estimated average requirement is thus *400 IU/day* of vitamin D for lactating women and adolescents. Available data do not indicate a basis for deriving upper limits for calcium and vitamin D for lactating women that are different from those for their non-lactating counterparts (*2,500 mg/day* calcium and *4,000 IU (100 μg)/day* vitamin D)
Oberhelman et al. 2013 PMID 3923377	Either single dose *(150000IU)* or daily maternal cholecalciferol *(5000IU)* can provide breast milk concentrations that result in vitamin D sufficiency in their infants. Larger trials demonstrating the safety of cholecalciferol supplementation in lactating mothers need to be

	conducted before universally adopting this strategy for preventing infant vitamin D deficiency.
VITAMIN K	
eMedicine.com 2014 Vitamin K Deficiency (Treatment)	The adequate intake for vitamin K for lactating women is *90 mcg/day*. These recommendations only fulfill the requirement for coagulation function.
SODIUM	
WHO 2012 Sodium intake for adults and children	WHO recommends a reduction in sodium intake to reduce blood pressure and risk of cardiovascular disease, stroke and coronary heart disease in adults to *<2 g/day* sodium (5 g/day salt) in adults (strong recommendation). This recommendation applies to all individuals, with or without hypertension, including lactating women.
ZINC	
EFSA 2014 Scientific Opinion on Dietary Reference Values for zinc	The population reference intake for zinc for adult women is *7.5-12.7 mg/day*. This is derived from zinc requirement of individuals with a body weight at the 97.5th percentile for reference weights for women. During lactation, zinc requirements are an *additional 2.9 mg/day*, related to transfer into breast milk.
OTHER	
EFSA 2014 Scientific Opinion on Dietary	Adequate intake for adults: *40 µg/day*. For lactating women, an *additional 5 µg/day*, is recommended to compensate for biotin losses

Reference Values for biotin	through breast milk. Mean concentrations of biotin in mature human milk measured by microbiological assays typically range between about 4 and 6 µg/L.
EFSA 2014 Scientific Opinion on Dietary Reference Values for chromium	The Panel concludes that no average requirement and no population reference intake for chromium can be defined, that there is no evidence of beneficial effects associated with chromium intake in healthy subjects, and that the setting of an adequate intake for chromium is also not appropriate
EFSA 2013 Scientific Opinion on Dietary Reference Values for fluoride	The adequate intake of fluoride from all sources (including non-dietary sources for both children and adults, including lactating women is *0.05 mg/kg/day*.
EFSA 2013 Scientific Opinion on Dietary Reference Values for manganese	The adequate intake of manganese for all adults, including lactating women is *3 mg/day*.
EFSA 2013 Scientific Opinion on Dietary Reference Values for molybdenum	The adequate intake of molybdenum for all adults, including lactating women is *65 µg/day*.
EFSA 2014 Scientific Opinion on Dietary	The average requirement for niacin for all adults, including lactating women is *1.3 mg NE/MJ (5.5 mg NE/1 000 kcal*, which is adopted by

Reference Values for niacin	the Scientific Committee for Food.
EFSA 2014 Scientific Opinion on Dietary Reference Values for pantothenic acid	The adequate intake for lactating women is *7 mg/day*, to compensate for pantothenic acid losses through breast milk.
EFSA 2014 Scientific Opinion on Dietary Reference Values for selenium	An adequate intake of *70 μg/day* for adults was set. Based on an average amount of selenium secreted in breast milk of 12 μg/day and an absorption efficiency of 70% from usual diets, an additional selenium intake of 15 μg/day was considered to replace these losses. Thus, an adequate intake of *85 μg/day* is proposed for lactating women.

Table 5: Documents on LC-PUFA supplementation during lactation -- summary of study results

Parameter		In reference	Time-point	Individual conclusion	Conclusion in meta-analysis Delgado	Meta-analysis based on
Weight:	**Short-term**	Helland et al. 2001 Jensen et al. 2005 Lauritzen et al. 2005 Hauner et al. 2012	6w, 3, 6, 9 & 2mo 3w, 2, 4, 8, 12mo 2, 4 & 9mo 6w, 4 & 12mo	No difference No difference No difference No difference	LC-PUFA supplementation: significant higher weight	Helland et al. Lauritzen et al. Hauner et al.
	Medium-term	Jensen et al. 2005 Lucia Bergmann et al.	18 & 24mo 21mo	No difference LC-PUFA supplementation: significant lower weight	LC-PUFA supplementation: significant lower weight	Lucia Bergmann et al.

		2007				
	Long-term	Jensen et al. 2010 Lauritzen et al. 2005 Helland et al. 2008 Asserhoj et al. 2009 Bergmann et al. 2012 Jensen et al. 2010	30mo 2.5y 7y 7y 6y 5y	No difference No difference No difference No difference No difference	No difference	Helland et al. Jensen et al. Asserhoj et al. Bergmann et al.
BMI:	**Short-term**	Lauritzen et al. 2005 Lucia	2, 4 & 9mo 1 &	No difference No difference No difference	No difference	Hauner et al.

		Bergman n et al. 2007 Hauner et al. 2012	3mo 6w, 4 & 12mo			
	Medium -term	Lucia Bergman n et al. 2007	21mo	LC-PUFA supplementation : significant lower weight	-'no studies reported on this outcome'	-
	Long-term	Lauritzen et al. 2005 Helland et al. 2008 Asserhoj et al. 2009 Bergman n et al. 2012	2.5y 7y 7y 6y	LC-PUFA supplementation : significant higher BMI No difference No difference No difference	No difference	Bergman n et al.
Fat mass &	**Short-**	Hauner et	6w, 4	No difference	No difference	Hauner et

Fat distribution:	**term**	al. 2012	& 12mo			al.
	Medium-term	None				
	Long-term	Lauritzen et al. 2005 Helland et al. 2008 Asserhoj et al. 2009 Bergman n et al. 2012	2.5 y 7 y 6 y 7 y	No difference No difference No difference No difference	No difference	Bergman n et al.

LC-PUFA; Long chain-polyunsaturated fatty acids. W; weeks. Mo; months. Y; years. BMI; body mass index.

Table 6: Research gaps identified by the authors of documents included

Reference	Further research / research gaps (if identified by the authors)	Notes/ Type of intervention discussed
Czech-Kowalska et al.	- Range of optimal 25(OH)D level in mothers - Amount of vitamin D during lactation to reach and maintain optimal 25(OH)D levels in mothers - Intervention study needed with higher vitamin D supplementation doses (1500IU/d vs. 2000IU/d vs. 3000 IU/d) in mothers	Vitamin D supplementation during lactation in women and infants
Ostadrahimi et al.	- Pilot study in the field, therefore further studies (in undernourished mothers) are needed	Synbiotic supplementation in lactating women
Aaltonen et al.	- Independent effect of maternal probiotic supplementation during lactation on infants' 32-33 high split proinsulin	Maternal dietary counselling, probiotic supplementation during pregnancy and lactation
Rodriquez et al.	- Mechanisms on the potential relationship between maternal n-3 LC-PUFA intake and infant growth	n-3 LC-PUFA supplementation in lactating women

	or later body composition	
Muhlhauser et al.	- Sufficiently powered studies, with appropriate controls, adequate blinding of participants and investigators, and high retention rates.	n-3 LC-PUFA supplementation in (pregnant &) lactating women
Koletzko et al.	- Control for baseline nutritional status and intakes, as well as genetic variation (e.g. the FADS genotype)	n-3 LC-PUFA supplementation in (pregnant &) lactating women
Martinez-Victoria et al.	- Randomized controlled trials with harmonized variables	n-3 LC-PUFA supplementation in (pregnant &) lactating women
Stratakis et al.	- High-quality trials are needed to establish whether n-3 LCPUFA supplementation in the perinatal period affects adiposity in children - Appropriate control regimen - Further explorement of sources of heterogeneity and effect modification	n-3 LC-PUFA supplementation in (pregnant &) lactating women
Campoy et al.	- Comparable results	n-3 LC-PUFA supplementation

	- Analysis of FADS gene	in (pregnant &) lactating women
Delgado et al.	- Standardization of techniques for measurements of different outcomes	n-3 LC-PUFA supplementation in lactating women
Hauner et al.	-	n-3 LC-PUFA supplementation and a reduced n6 LC-PUFA intake in (pregnant &) lactating women.
Bergmann et al.	- Large studies with long observation periods, combined with genetic tests. - Comparable study designs	n-3 LC-PUFA supplementation in (pregnant &) lactating women.
Jensen et al.	- Mechanisms underlying long-term benefits of early nutritional interventions	n-3 LC-PUFA supplementation in lactating women.

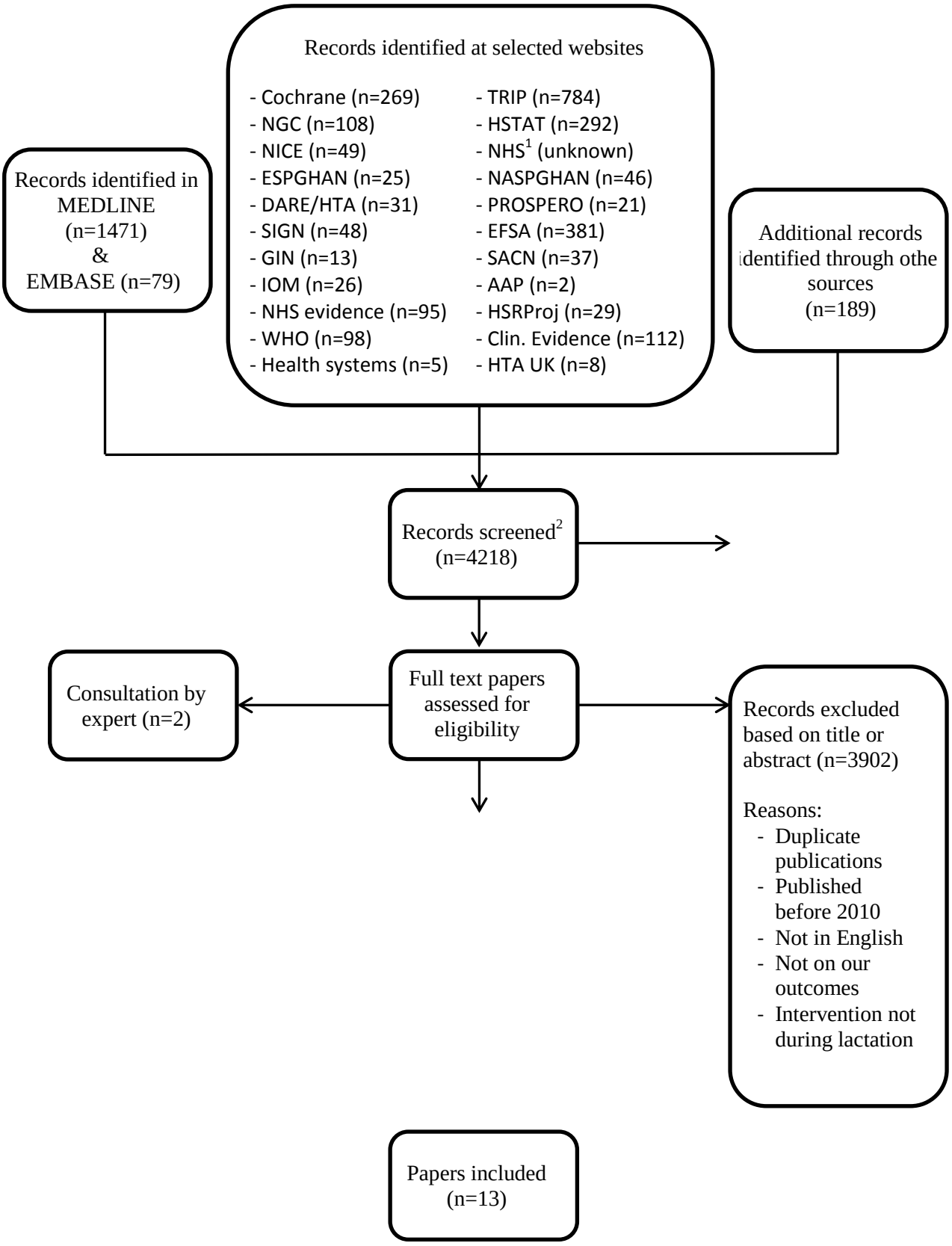

Figure 1. Flowchart of study selection process [1]No access to this database outside Great-Britain. [2]Duplicates within one database or at one website were identified and excluded from the number of screened records, duplicates between databases or websites were not.

