Scientific Advisory Committee on Nutrition

‘Feeding young children aged 1 to 5 years’

—

Annex 5

Contents

Annex 5: Evidence tables

Energy and Macronutrients

Table A5.1 Evidence table – energy and macronutrients

Study	Methods	Included studies	Results	Comments
Hörnell et al (2013) 'Protein intake from 0-18 years of age and its relation to health: a systematic literature review for the 5th Nordic Nutrition Recommendations' <u>Funding</u> Nordic Council of Ministers <u>Declaration of interest</u> None to declare	<u>Research question</u> What are the effects of different intakes and different sources of protein (animal- or plant-based) in infancy and childhood, while considering other energy-giving nutrients on: 1) functional or clinical outcomes, including growth and development? 2) well-established markers or indicators of functional or clinical outcomes, such as serum lipids, glucose and insulin, blood pressure, body weight, body composition and bone mineral density, in childhood, adolescence and adulthood? <u>Search criteria</u> *Search dates:* January 2000 to February 2012 *Search design*: human studies *Population:* healthy children from a study population relevant to the Nordic countries *Intervention or exposure:* different intakes and different sources of protein (animal or plant-based) <u>Primary outcomes</u> - Growth and body composition, for example, BMI, % body fat (%BF), adiposity rebound (AR) and sIGF-I	<u>Number of studies</u> 38 studies (9 trials, 21 PCS, 8 CS), of which 13 studies (reporting on 9 PCS) included participants aged 12 to 60 months at baseline. <u>Number of participants</u> Of the 13 studies of interest, 3 included fewer than 100 participants, 7 had 100 to 300 participants, 3 had 450 to 950 participants, and 1 had nearly 3300 participants. <u>Age of participants</u> Most of the 13 studies of interest included children aged 6 to 24 months at baseline, with most follow-up until age 5 to 8 years (1 up to 18 years old). <u>Countries</u> High income countries, including UK	<u>Results of interest for the age group covered in this report</u> (Total) protein intake and BMI and body composition (%BF) (5 publications reporting on 4 PCS) - all 5 PCS (2 in the same cohort) reported a direct association (see Annex 9, Table A9.7 for details) (Total) protein intake and adiposity rebound (AR) (3 PCS) - all 3 PCS reported no association between protein intake and timing of AR (see Annex 9, Table A9.8 for details) Animal protein intake and growth (1 PCS) - the PCS reported that a direct association (see Annex 9, Table A9.8 for details) Total and animal protein intake and puberty (4 studies, 2 from same cohort, DONALD) – all 4 PCS reported an association between total or animal protein intake and earlier onset of puberty (see Annex 9, Table A9.9 for details)	<u>Risk of bias or quality</u> - Study quality assessed using QAT, which includes questions about study design, population characteristics, exposure and outcome measures, dietary assessment, and confounders. - Studies were rated A (low risk of bias), B, or C (high risk of bias). Studies graded C were not used in the final grading of the evidence and were not reported in evidence tables. - Evidence graded 'convincing' (grade 1), 'probable' (grade 2), 'limited-suggestive' (grade 3), and 'limited-inconclusive' (grade 4) depending on the number and quality of supporting, non-supporting, and contradicting studies. <u>Limitations</u> (from the authors) - When papers originated from the same research group, it was not always possible to tell whether the participating children were the same in several studies. This is problematic as evidence grading requires evidence from at least two independent cohort studies

Study	Methods	Included studies	Results	Comments
	- Bone health (bone mineral content, BMC or bone mineral density, BMD) - Puberty timing - Glucose-insulin metabolism - Blood pressure - Neurodevelopment	<u>Exposure</u> The majority of the 13 studies of interest reported protein intakes or energy-adjusted protein intakes (g per day or % energy or g or kg of reference body weight per day). 1 study reported total red and white meat intake. A couple of studies also reported intakes of different types of protein (animal compared with vegetable).	Vegetable protein intake and puberty (2 PCS) – both PCS reported an inverse association (see Annex 9, Table A9.9 for details) Protein intake and bone health (1 PCS) - 1 PCS reported a direct association between protein intake and BMD and BMC (see Annex 9, Table A9.10 for details) Protein intake and neurodevelopment (2 PCS) - Both PCS reported a direct association between protein intake and neurodevelopment (see Annex 9, Table A9.10 for details) sIGF-I; glucose-insulin metabolism; blood pressure - No trials or PCS in children aged 1 to 5 years identified for these outcomes.	(the authors took this into account in their grading). - Many of the included studies do not differentiate between the effects of protein and other properties of the protein source (for example, dairy products) <u>AMSTAR 2 overall confidence rating:</u> moderate
Naude et al (2018) 'Effects of total fat intake on bodyweight in children' <u>Funding</u> World Health Organisation <u>Declaration of interest</u> Authors part supported by the Effective Healthcare Research Consortium, UK, which is funded by UK aid	<u>Research question</u> To assess the effects of total fat intake on measures of weight and body fatness in children and young people not aiming to lose weight. <u>Search criteria</u> *Search dates:* to May 2017 *Search design:* RCTs and cohort studies *Population*: children and young people (aged 24 months to 18 years) with or without risk factors for cardiovascular disease; children who were acutely ill as well as disease- or condition-specific populations, such as children	<u>Number of studies</u> 24 studies (3 RCTs and 21 PCS), of which 6 PCS included participants aged 12 to 60 months at baseline. <u>Number of participants</u> Of the 6 PCS of interest, sample sizes ranged from 53 to 740, with most studies including 100 to 250 participants. <u>Age of participants</u>	<u>Results of interest for the age group covered in this report</u> <u>Primary outcomes</u> Total dietary fat and body weight (2 PCS) - both PCS reported no association between dietary fat intake and body weight. Total dietary fat and BMI (5 PCS) - 2 of 3 PCS reported a direct association after 2 to 3 years of follow-up. 1 of 3 PCS reported no association. 2 of 2 PCS reported a direct association after 6 to 14 years follow-up.	<u>Risk of bias or quality</u> - RCTs assessed using the Cochrane tool; 'other bias' consisted of whether trials were free of differences in diet between intervention and control groups other than dietary fat intake. - PCS assessed using Cochrane methodology, including matching of more-exposed and less-exposed groups, whether groups differed in components other than total fat, ascertainment of exposures and outcomes, assessment of prognostic factors.

Study	Methods	Included studies	Results	Comments
from the UK government for the benefit of developing countries.	with cystic fibrosis, autism or diabetes, were excluded. Intervention studies where the selection of participants was primarily for raised weight or BMI with the intention to reduce weight were excluded. *Intervention or exposure and comparator:* - RCTs: lower fat intake compared with usual diet or modified fat intake with no intention to reduce weight (in any groups), continued for at least 6 months unconfounded by non-nutritional interventions - cohort studies: total dietary fat intake (in grams, as % total dietary energy intake or as one of the defining characteristics of a dietary pattern) assessed at baseline and related to a measure of body fatness, or change in body fatness, at least one year later. <u>Primary outcomes</u> - Measure of body fatness at least 6 months after the intervention was initiated (RCTs) - Absolute or change in body fatness at least one year later (PCS) <u>Secondary outcomes</u> - Cardiometabolic risk factors (LDL, HDL cholesterol, TAG, systolic and diastolic blood pressure) - Height <u>Statistical analysis</u> - Meta-analysis, subgroup analysis (to investigate heterogeneity) and sensitivity analysis were planned but not all were undertaken due to the diversity of methodologies, analysis methods, dietary assessments, ages	Of the 6 PCS of interest, participants were aged between 2 and 4.5 years old at baseline, with follow-up durations of 1 to 17 years. <u>Countries</u> High income countries	Association between total dietary fat exposure and body fat or fat mass index (1 PCS) - the PCS reported a direct association For details see Annex 9, Table A9.3. <u>Secondary outcomes</u> Association between total dietary fat exposure and height (2 PCS) - neither study reported any association between total dietary fat and height after 1 to 2 years follow up. (See Annex 9, Table A9.6 for details) No studies in children aged 12 to 60 months were identified that assessed the relationship between total fat intake and cardiometabolic risk factors.	- GRADE system used to rank the quality of evidence. <u>Limitations</u> (from the authors) - GRADE assessments for cohort studies on primary outcomes very low therefore confidence in the validity of the findings was limited. - Evidence on the link between dietary fat intake and body fatness in non-obese children across systematic reviews was sparse. <u>AMSTAR 2 overall confidence rating:</u> high

Study	Methods	Included studies	Results	Comments
	at baseline, applications of total fat intake exposure and eligible outcome measures. None of these analyses were undertaken using studies with children aged 12 to 60 months.			
Parsons et al (1999) 'Childhood predictors of adult obesity: a systematic review' Funding Department of Health or Medical Research Council Nutrition Research Initiative Declaration of interest None declared	Research question To identify factors in childhood which might influence the development of obesity in adulthood. Search criteria *Search dates:* up to Spring 1998 *Study design:* longitudinal observational studies; studies that were <1 year in duration were excluded *Population:* healthy children (<18 years old) from industrialised countries; studies on minority or special groups (for example, vegans, children born preterm or to diabetic mothers) were excluded. *Intervention or exposure and comparators:* measurements of predictors of obesity (including diet and physical activity [PA]) Primary outcome Any measure of fatness, leanness or relative weight, or change in fatness, leanness or relative weight (measured at least 1 year after exposure assessment); measures of fat distribution were not included.	Number of studies 8 PCS (reported in 12 publications) on child dietary intake, of which 4 PCS (reported in 5 publications) included measurements at ages 12 to 60 months. To note, 2 PCS were reported in the SR by Naude et al (2018) on total dietary fat intake and bodyweight in children. Number of participants The 4 PCS included between 37 and 450 participants. Age of participants Of the studies of interest, children were aged >6 months at baseline and followed-up until age 6 to 15 years. Countries High income countries	Results of interest for the age group covered in this report Child dietary intake and fatness in later childhood (4 PCS reported in 5 publications) Energy intake (3 PCS, reported in 4 publications) Of the 3 PCS, 1 reported a direct association between energy intake and body fatness, and 2 reported an inverse association (in one of these studies, the association was found in girls only). (See Annex 9, Table A9.1 for details) Total carbohydrates (2 PCS) - Both PCS reported no association between total carbohydrate intake and BMI or skinfolds. (See Annex 9, Table A9.2 for details) Dietary fat (1 PCS) – the PCS reported no association between dietary fat intake and BMI or skinfolds. (See Annex 9, Table A9.3 for details) Protein (1 PCS) - 1 PCS reported a direct association between protein intake and BMI or skinfolds (See Annex 9, Table A9.7 for details)	Risk of bias or quality Study quality not formally assessed due to difficulties in developing quality criteria for a heterogeneous group of studies. However, limitations of studies identified were discussed in each section of the review. Limitations (from the review authors) - All studies of interest were small and conducted between 1984 and 1998 AMSTAR 2 overall confidence rating: critically low
Perez-Morales et al (2013)	Research question	Number of studies	Results from the PCS uniquely identified by this SR	Risk of bias or quality

Study	Methods	Included studies	Results	Comments
'Sugar-sweetened beverage intake before 6 years of age and weight or BMI status among older children; systematic review of prospective studies' Funding Not specified Declaration of interest Not specified	To conduct a systematic review of prospective studies that examined the association between SSB intake before six years of age and later weight or BMI status among older children. Search criteria *Search dates:* 2001 to 2011 *Study design:* prospective cohort studies *Population*: children < 6 years old *Exposure and comparators:* intake of SSB, including soft drinks, soda, fruit drinks, sports drinks, sweetened iced tea, and lemonade Primary outcome Body weight, BMI, waist circumference	7 PCS, of which 1 PCS was uniquely identified by and included in this SR (see Annex 6, Table A6.1 for mapping of primary studies) Number of participants The PCS included 135 participants Age of participants Participants were aged 3 to 5 years at baseline and followed up for 3 years Countries High income countries	The PCS reported that SSB consumption was directly associated with child waist circumference (see Annex 9, Table A9.2 for details).	- No formal tool was used to assess risk of bias; the review authors only commented that 2 of the studies had less risk of bias than the others. AMSTAR 2 overall confidence rating: critically low
Rouhani et al (2016) 'Associations between dietary energy density and obesity: A systematic review and meta-analysis of observational studies' Funding The Research Council of the Food Security Research Center, Isfahan University of Medical Sciences Declaration of interest Not specified	Research question To examine whether evidence from observational studies overall show a direct link between dietary energy density (DED) and obesity, and to calculate an estimate of the risk. Search criteria *Search dates:* up to January 2015 *Study design:* observational studies *Population:* children (>2 years old) and adults (≤60 years old) *Exposure and comparators:* DED; studies that did not consider DED for the whole diet were excluded Primary outcomes	Number of studies 37 studies included (22 CS and 15 PCS), of which 2 PCS were conducted in participants aged 12 to 60 months at baseline (not included in the MA). The SR reported CS analyses for 1 of the PCS. Therefore, data from this PCS was not extracted in Annex 9, Table A9.1. Number of participants The PCS of interest included 589 participants Age of participants	Results of interest for the age group covered in this report 1 PCS (reported not association between DED and BMI z-score Food and beverages were used to calculate DED (as opposed to solid foods only or food and selected beverages for example, milk or energy-containing beverages) (See Annex 9, Table A9.1 for details)	Risk of bias or quality Newcastle-Ottawa Scale was used to score the quality of studies included in the MA only; the PCS of interest was not scored as these were not included in the MA. Limitations (from the authors) Increased adiposity is a better predictor of obesity than BMI, which has several limitations (for example, BMI fails to take into account the difference between fat and muscle mass. AMSTAR 2 overall confidence rating: critically low

Study	Methods	Included studies	Results	Comments
	Obesity Statistical analyses - Random-effects model - Between-study heterogeneity and between-subgroup heterogeneity was evaluated by I^2 and fixed-effect models, respectively. - Sensitivity analyses performed to evaluate the contribution of each study on the overall effect - Publication bias calculated using Begg's adjusted rank correlation test.	Participants were age 3 years at baseline and followed up for 3 years Countries High income countries		
Voortman et al (2015a) 'Effects of polyunsaturated fatty acid intake and status during pregnancy, lactation and early childhood on cardiometabolic health: a systematic review' Funding Nestle Nutrition (Nestec Ltd), Metagenics Inc and AXA Declarations of interest None	Research question What are the effects of PUFA intake and blood levels during pregnancy, lactation, or in early childhood up to the age of 5 years on cardiometabolic health? Search criteria *Search dates:* until 1 April 2014 *Study design:* intervention, cohort, CC or CS *Population:* exposure measure or intervention in healthy pregnant or lactating women, or in healthy children aged ≤5 years (outcome measures in the offspring at any age) *Exposure and comparators:* intake or blood levels of PUFAs, including total PUFAs, total n-3 FAs, total n-6 FAs, ratios between n-6 and n-3 FAs, fish oil, eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), docosahexaenoic acid (DHA), linoleic acid (LA), gamma-linolenic acid (GLA),	Number of studies 45 studies (19 trials, 24 PCS, 1 retrospective cohort study and 3 CS) reported in 56 publications, of which 2 RCTs and 7 PCS (reported in 8 publications) included children aged 12 to 60 months at baseline. Number of participants The 2 RCTs of interest included 100-133 participants; of the 7 PCS of interest 1 included <100 participants, 5 included between 100-500 participants and 1 included >2,500 participants. Age of participants Participants in the studies of interest were aged 6	Results of interest for the age group covered in this report Association between PUFAs and measures of obesity (3 PCS) - 1 of 3 PCS reported an association between PUFA intake and a measure of obesity; 2 of 3 PCS reported no association (see Annex 9, Table A9.3 for details) n-3 FAs and BMI (2 RCTs, 1 PCS) - Neither RCT reported a significant effect of n-3 FA intake on BMI; the PCS also reported no association between n-3 FA and BMI (see Annex 9, Table A9.3 for details) PUFAs and blood lipids (1 RCT and 2 PCS) 1 PCS reported an inverse association between PUFA intake and HDL-C only. There was no reported relationship with all other outcomes examined (including total cholesterol, LDL-C, triacylglycerol) (see Annex 9, Table A9.4 for details)	Risk of bias or quality - Study quality assessed using a predefined scoring system based on guidelines from the American Heart Association and American Diabetes Association. The scoring system has 5 items including study design, population size, exposure assessment or appropriate blinding of an intervention, and adjustment for potential confounders or adequate randomisation of an intervention. Quality score (QS) range is 0 to 10, with 10 representing the highest quality. AMSTAR 2 overall confidence rating: low

Study	Methods	Included studies	Results	Comments
	dihomo-gamma-linolenic acid (DGLA), arachidonic acid (ARA) <u>Primary outcomes</u> Cardiovascular and metabolic outcomes, including obesity (BMI, weight-for-height, body fat), blood pressure (BP), blood lipids (TAG and total cholesterol, HDL and LDL cholesterol), measures of insulin sensitivity (glucose or insulin levels, HOMA, T2DM)	months to 5 years at exposure, with most studies including children aged 12 to 18 months. Mean age at follow-up ranged from 1 to 5.8 years. <u>Countries</u> High income countries, including 1 in the UK <u>Exposure</u> Of the 9 studies of interest, 8 reported dietary n-3, n-6 or mixed PUFA intakes (%E, g per day, energy-adjusted g per day, %fat). - 1 PCS reported n-3 FA levels and n-6 or n-3 FA ratio in plasma phospholipids. - Of the 2 RCTs of interest, the intervention group in one trial received 1.6g fish oil for 9 months (compared with sunflower oil), while the intervention group in the other trial received 500mg of DHA + EPA from oils, spreads and infant formula.	PUFAs and blood pressure (1 trial, 1 PCS) - Neither study reported a relationship between PUFA intake and blood pressure (see Annex 9, Table A9.5 for details) No studies were identified in children aged 12 to 60 months that assessed the relationship between dietary PUFA or blood PUFA and measures of insulin sensitivity. The review authors concluded that "there was no clear detrimental or beneficial effects of PUFA intake or blood levels in pregnancy, during lactation, or in early childhood on obesity, blood pressure or blood lipids in children".	
Voortman et al (2015b) 'Effects of protein intake on blood pressure, insulin sensitivity and blood	<u>Research question</u> What are the associations of protein intake and blood pressure, insulin sensitivity and blood lipids in children? <u>Search criteria</u> *Search dates:* until 31 May 2013	<u>Number of studies</u> 56 studies (reported in 60 papers), of which 1 PCS included participants aged 12 to 60 months. <u>Number of participants</u>	<u>Results of interest for the age group covered in this report</u> Protein intake and blood lipids The PCS of interest reported no association between protein intake and any of the blood lipids examined (total cholesterol, LDL-C, HDL-C,	<u>Risk of bias or quality</u> - Quality of RCTs and cohort studies assessed using a 5-item questionnaire based on guidelines from the American Heart Association and American Diabetes Association. Items

Study	Methods	Included studies	Results	Comments
lipids in children: a systematic review' <u>Funding</u> Nestle Nutrition (Nestec Ltd), Metagenics Inc, and AXA <u>Declarations of interest</u> None to declare	*Search design:* CS, CC, cohort and intervention studies *Population:* children ≤18 years old; children with congenital diseases, phenylketonuria, type 1 diabetes or kidney disease were excluded *Intervention or exposure:* total, animal or vegetable protein intake <u>Primary outcomes</u> - BP: systolic or diastolic BP (mmHg); mean arterial pressure; hypertension - Insulin sensitivity: insulin levels; glucose levels; glucose tolerance; HOMA-IR; T2DM - Blood lipids: TC; HDL-C; LDL-C; TAG	The PCS of interest included 389 participants <u>Age of participants</u> Participants were age 18 months at baseline and followed up at age 31 months <u>Countries</u> High income countries	triacylglycerol) (see Annex 9, Table A9.10 for details) Protein intake and other health outcomes No studies in children aged 12 to 60 months identified	included study design, study size, exposure assessment, outcome assessment, adjustments for potential confounders or randomisation. The maximum possible quality score = 10. 'Higher quality' studies scored ≥6. - Evidence graded as 'strong', 'moderate', 'limited' or 'insufficient' depending on the number of studies, quality and consistency. <u>AMSTAR 2 overall confidence rating:</u> low

Micronutrients

Table A5.2 Evidence table – micronutrients

Study	Methods	Included studies	Results	Comments
Athe et al (2014) 'Impact of iron-fortified foods on Hb concentration in children (< 10 years): a systematic review and meta-analysis of randomized controlled trials' Funding National Institute of Nutrition (NIN), Indian Council of Medical Research, Hyderabad, India Declaration of interest None to declare	Research question To combine evidence from RCTs to assess the effect of iron-fortified foods on mean Hb concentration in children (<10 years). Search criteria *Search dates:* 1990 up to December 2010 *Search design:* RCTs *Population*: children aged <10 years *Intervention and comparator:* various levels of iron fortification (including multiple intervention groups with other micronutrients administrated simultaneously) Primary outcome Hb concentration Statistical analyses - Random effect model. - Heterogeneity: *Q* statistic, variance (T^2) between studies, and I^2 parameter. - Publication bias: funnel plot and Egger regression test.	Number of studies 18 studies, of which 10 had participants aged 12 to 60 months at baseline. Number of participants 5142 participants included in MA Age of participants Mean age 4.7 years (SD 3.0) Countries Mainly Lower Middle Income Countries (LMIC) Intervention - Daily iron intake through fortified food ranged between 3.5 and 12.7 mg per child, with intervention duration ranging between 4 and 24 months. - Half of the studies of interest used drinks as a food vehicle (milk: 2, water: 2, orange juice: 1), 3 used staples (maize, rice or rice-based dish) and 2 used snacks. The Fe compound used was mainly ferrous sulphate.	Main results as reported in the SR Hb concentration (18 studies, n=5142) - Mean change significantly higher in the Fe-fortified group than in the control: WMD 5.09g/l (95% CI 3.23 to 6.95; p<0.00001). - No adverse effect reported. - Meta-regression: duration of intake of fortified food is an effective confounder. - After removal of confounders (including study duration): WMD 4.74g/l (95% CI 3.08 to 6.40). - Probable absence of publication bias. Significant heterogeneity	Risk of bias or quality - Individual study quality assessed, probably based on Cochrane Handbook, but details provided only on 2 criteria (concealment of allocation and blinding) - No additional information or discussion provided on study quality, except in the conclusion were a need for higher quality and more rigorous randomised controlled trials was highlighted. Confounding factors - The influence of confounding factors such as age, duration of intervention and levels of fortification was assessed through meta-regression analysis. - Duration of intervention was identified as a confounder (details not reported). Limitations (from the review team) Findings were not stratified by baseline nutritional status AMSTAR 2 overall confidence rating: low

Study	Methods	Included studies	Results	Comments
Das et al (2013) 'Micronutrient fortification of food and its impact on woman and child health: a systematic review' Funding Not specified Declaration of interest None to declare	Research question To assess the effectiveness of food fortification with single micronutrients (iron, folic acid, vitamin A, vitamin D, iodine, zinc, calcium) as well as multiple micronutrients (MMN) when compared with no fortification on the health and nutrition of women and children. Search criteria *Search dates:* up to November 2012 *Search design:* RCTs, quasi-experimental and before-after studies; other studies designs (for example, observational) were also reviewed to understand the context of these interventions *Population*: infants, children, adolescents <18 years old (and women of reproductive age and post-menopausal women) *Intervention:* impact of fortification intervention with a single, dual or multiple micronutrients administrated through 3 food vehicles: staples, condiments, or processed foods (excluded: home fortification, biofortification, comparison between fortification and supplementation, etc) *Comparators:* unfortified foods or regular diet Primary outcomes - biochemical indicators (for example, serum micronutrient levels) - haematologic markers (anaemia, IDA, Hb) - anthropometric indicators (stunting, wasting, underweight, and changes in height and weight z-scores)	Number of studies 201 studies (125 RCTs, 7 quasi experimental and 69 before-after studies). Although subgroup analyses were conducted in preschool and school children (aged 2 to 18 years) for most intervention groups (single and multiple micronutrients), only findings from MAs on vitamin A fortification were substantially weighted towards children aged 12 to 60 months (>50% weighting of MAs. Therefore, only findings on vitamin A fortification were extracted here and in Annex 9, Tables A9.19 and 8.21. Countries High Income countries (HIC), upper middle income countries (UMIC), lower middle income countries (LMIC) Intervention Vitamin A - food vehicle: biscuits, monosodium glutamate, sugar, flour and seasoning. - Duration: all studies >6 months.	Results of interest for the age group covered in this report Vitamin A fortification Hb levels (SMD; GRADE: low) - Combined effect: (0.48; 95% CI: 0.07 to 0.89; I^2=93%; 2 studies, 1538 participants of which 1 study, with 73.5% weighting in the MA, included children aged 3 to 6 years) Serum vitamin A concentration (SMD; GRADE: low) - Combined effect: (0.61; 95% CI: 0.39 to 0.83; I^2=84%; 3 studies, 2362 participants, of which 1 study, with 55.5% weighting in the MA, included children aged 3 to 6 years) Vitamin A deficiency (RR; GRADE: moderate) - Combined effect: (RR 0.39; 95% CI 0.09 to 1.74; p=0.22; I^2=88%; 2 studies, 1465, of which 1 study, given 70.9% weighting in the MA, included children aged 3 to 6 years) See Annex 9, Tables A9.18 and A9.20 for more details.	Risk of bias or quality - Risk of bias assessed through Cochrane Collaboration tool, including sequence generation, allocation concealment, blinding and selective outcome. - GRADE approach used to assess the quality of the evidence for each outcome. Confounding factors - The review authors reported that limited information was available on confounding factors such as age and nutritional status. Limitations (from the authors) - As large-scale fortification programs are usually before-after studies, a range of studies of varying sizes and scientific rigour had to be included, resulting in many limitations. - Foods used, micronutrient concentrations, frequency of intakes, and duration of the intervention periods varied across studies - Limited information available on the impact of fortification on anthropometric measures, morbidity and mortality, which are essential to evaluate future benefits and effective strategies. Limitations (from the review team) - Although the review authors declared that they had no competing interests, they noted that they "are grateful to the Nestle Nutrition Institute for its

Study	Methods	Included studies	Results	Comments
	- relevant morbidity and mortality definition used: • anaemia: 6-59 months: Hb<110g/l • vitamin A deficiency: plasma (serum) retinol concentration <20µg/dl • zinc deficiency: serum zinc concentration <10.7µmol/l • asymptomatic zinc deficiency: <10.7µmol/l without clinical signs or symptoms. Statistical analyses - Separate MA performed for RCTs or quasi experimental studies, and before-after studies (results of before-after MA were reported only if no RCTs or quasi-experimental studies were available). - Random-effects model - Heterogeneity: I^2 statistic, chi-square test and visual inspection of forest plots. - Subgroup analyses: age groups, countries, population characteristics, type of food fortified, and duration of intervention.			unrestricted support towards the genesis of this review and its external assessment in an advisory group meeting in Zurich in October 2011". - Multiple planned subgroup analyses were not reported or performed - Risk of publication bias was not investigated. - Findings were not stratified by baseline nutritional status AMSTAR 2 overall confidence rating: critically low
De-Regil et al (2011) 'Intermittent iron supplementation for improving nutrition and development in children under 12 years of age' Funding *Internal sources*: Centers for Disease Control and Prevention (CDC), US, and World	Research question To assess the effects of intermittent iron supplementation, alone or in combination with other vitamins and minerals, on nutritional and developmental outcomes in children less than 12 years of age compared with daily supplementation, a placebo or no supplementation. Search criteria *Search dates*: up to June 2011. *Study design*: Randomised and quasi-randomised trials with either individual or cluster randomisation	Number of studies 33 trials included, 20 included participants aged under 5 years. Of the 20, 13 included participants aged 12 and 60 months. Countries Lower middle income countries (LMIC) Interventions - Most of the trials (including the 13 of interest) provided weekly	Results of interest for the age group covered in this report See Annex A9.12 for details	Risk of bias or quality - Risk of bias assessed using the criteria outlined in the Cochrane Handbook for systematic reviews of interventions. - The authors considered that indirectness or publication bias was unlikely but the quality of the trials and inconsistency (or the lack of studies) were potentially important factors in the overall assessment of the evidence. Confounding factors

Study	Methods	Included studies	Results	Comments
Health Organization (WHO), Switzerland. *External sources*: 1 author received partial financial support from WHO for this review, and the WHO received financial support from the Government of Luxembourg for conducting SR on micronutrient interventions. <u>Declaration of interest</u> None to declare. *Disclaimer*: 3 of the authors have worked or received financial support from the WHO and the 4th author is a full-time staff member of the CDC.	*Population*: children under the age of 12 years at the time of intervention with no specific health problems *Interventions*: intermittent iron supplementation compared with a placebo, no intervention or daily supplementation; iron supplements combined with co-intervention were included if the co-intervention was the same in both the intervention and the control groups *Comparators*: 6 different comparisons were performed, 2 of them for children aged 0 to 59 months: any intermittent iron supplementation versus no supplementation or placebo, and versus daily iron supplementation <u>Primary outcomes</u> - Anaemia (haemoglobin below a cut-off defined by trialists) - Haemoglobin (g/l) - Iron Deficiency (as measured by trialists by using indicators of iron status, such as ferritin or transferrin) - Iron status (ferritin in µg/l) - Iron Deficiency Anaemia (defined by the presence of anaemia plus iron deficiency, diagnosed with an indicator of iron status selected by trialists) - All cause mortality (number of deaths during the trial) <u>Meta-analysis</u> - Random-effects model - For outcomes with 4 trials or more, subgroup analysis carried out to investigate heterogeneity (I^2). Subgroups included weekly dose of iron, duration of supplementation, type of compound, anaemia status at baseline, intermittent supplementation	doses between 25 and 75mg of elemental iron, either alone, with folic acid or with other micronutrients (for example vitamins A, C or D, or zinc). - Nearly half of the trials had a duration of 3 months or less, and half of more than 3 months.		- The authors noted that in some studies there was some baseline imbalance on potential confounders in terms of participants characteristics. <u>Limitations</u> (from the authors) - 75% of the included trials had a sample size of less than 500 children and the trials often lacked blinding and a clear description of randomisation methods. - Baseline anaemia and iron deficiency status varied across studies; most were conducted in settings with a high prevalence of anaemia. - Insufficient studies to allow the authors to evaluate in detail all the outcomes of interest and by subgroups. - Lack of data to meaningfully examine adherence and adverse effects specifically related to intensity and frequency of dosing. <u>Limitations</u> (from the review team) - It was not possible to disaggregate findings in children younger and older than 12 months of age. <u>AMSTAR 2 overall confidence rating</u>: high

Study	Methods	Included studies	Results	Comments
	regimen, participants sex, and micronutrient composition. - Sensitivity analysis carried out to examine the effects of high risk of bias studies.			
Domellöf et al (2013) 'Health effects of different dietary iron intakes: a systematic literature review for the 5th Nordic Nutrition Recommendations' Funding The Nordic Council of Ministers Declaration of interest None to declare	Research questions (1) What is the minimal dose of dietary iron intake that will prevent poor functional or health outcomes in different age groups within the general population including the risk groups for ID? (2) What is the highest dose of dietary iron intake that is not associated with poor functional or health outcomes in different age groups within the general population including some risk groups for iron overload? Search criteria *Search dates*: January 2000 to December 2011 *Study design*: published papers, excluding letters, news article, congress reports and non-systematic review *Population*: No limitation on age (infants, children, pregnant women and adults included), healthy humans of relevance to the research question; population relevant for Nordic countries (excluding populations from LMIC in Africa, South America and Asia) *Intervention and comparator*: 'of relevance to the research questions' Primary outcomes - Anaemia - Cognitive or behavioural function - Growth and development	Number of studies 55 articles, 3 included participants aged 1 to 5 years (2 PCS and 1 SR with MA – Ramakrishnan et al, 2009, which was separately identified and included in this report). Age of participants Up to 24 months for the 2 PCS, up to 5 years for the SR or MA. Number of participants Total not specified. n=74 and 94 for the 2 cohort studies. 27 trials included in the SR or MA. Countries Mostly high income countries (HIC) Interventions - In 1 PCS, the exposure was dietary iron intake and the outcome was prevalence of IDA; in the other PCS, the exposure was dietary iron intake and cows' milk intake and the outcome was iron status. - In the SR or MA, intervention was iron	Results of interest for the age group covered in this report Anaemia and iron status – young children (2 PCS) - Both PCS reported a lower iron intake than recommended in children aged 9 to 24 months, but the prevalence of IDA was low at age 24 months. - 1 PCS reported a significant association between cows' milk intake >500mlday and ID (50% compared with 2%, p<0.001). Child growth (1 MA) No significant effect of iron supplementation on growth in children <5 years of age (but children were not stratified by initial iron status). Physical performance; cognitive and behavioural function; hypertension and cardiovascular disease; diabetes mellitus; cancer No studies conducted in young children were identified. Other results The SR also reported on the interactions between iron and other food components - No conclusive evidence (in all age groups) that iron supplements affect zinc or copper absorption. - Tea (in 2 reviews that included 6 studies in infants and children, n=2942). No need to advise any	Risk of bias or quality - Study quality assessed using QAT, which includes questions about study design, recruitment, compliance, dietary assessment, confounders, statistics and outcomes. - Studies were graded A (low risk of bias), B or C (high risk of bias). Studies graded C were not used in the final grading of the evidence and were not reported in evidence tables. Confounding factors - Most of the studies on infants and children (included the 3 of interest) did not report on confounding factors. Limitations (from the authors) None reported. Limitations (from the review team) - In relation to the grading of evidence, only the final grade (A, B, C) was provided for each reference, without details about which bias had each study. - The authors assessed and graded the evidence for both infants and children, as one group. It was therefore not possible to report a grading of the evidence for young children only. - Findings were not stratified by baseline nutritional status

Study	Methods	Included studies	Results	Comments
	- Adverse effects, including the possible risk of cancer and cardiovascular disease	supplementation, with most common dose being 10 mg per day and duration between 2 and 12 months.	restrictions on tea drinking in healthy people with no risk of ID. In groups at risk of ID, the advice should be to drink tea between meals (at least 1h after eating).	AMSTAR 2 overall confidence rating: low
Eichler et al (2012) 'Effect of micronutrient fortified milk and cereal food for infants and children: a systematic review' Funding Supported by the Nestle Nutrition Institute Declaration of interest None to declare	Research question To specifically assess the impact of micronutrient fortified milk and cereal food on the health of infants and children compared to non-fortified food in RCTs. Search criteria *Search dates:* up to February 2011 *Search design:* RCTs of any follow-up time *Population*: infants and children from 6 months to 5 years of age (primary focus was up to 2 years old, but higher upper limit was set in order not to miss suitable studies with mixed age groups) *Intervention and comparators:* micronutrient fortified milk or cereal foods *Comparators:* non-fortified food; additional other nutritional approaches if such approaches were applied in both groups Primary outcomes - Micronutrient serum levels - Haematological parameters - Functional outcomes (for example, motor development)	Number of studies 18 studies, of which 6 had participants aged 12 to 60 months at baseline (mean age at baseline <12 months for the 12 other studies). Mean age at inclusion ranged from 6 to 23 months (upper age limit was 3 years in 1 study). Only findings from MAs on vitamin A fortification were substantially weighted towards children aged 12 to 60 months (>50% weighting of MAs. Therefore, only findings on vitamin A fortification were extracted here and in Annex 9, Table A9.18. Countries Mainly upper middle income countries (UMIC) and lower middle income countries (LMIC) Intervention - Most participants belonged to vulnerable groups and were recruited from different settings (for	Results of interest for the age group covered in this report Effect of vitamin A (dual and multiple micronutrient) on retinol levels (4 RCTs, aged 6m to 3 years at baseline) - 3.7µg/dl; 95% CI 1.3 to 6.1; I^2=37%; 4 RCTS, participants and interventions NR, % weighting in children aged 1 to 5 years NR) See Annex 9, Table A9.18 for details.	Risk of bias or quality - Risk of bias assessed through Cochrane Collaboration tool, including generation of random sequence, allocation concealment, blinding, incomplete outcome data due to attrition, and selective outcome. Confounding factors - The authors did not comment on confounding factors. - A multivariable meta-regression analysis was performed but not on outcomes relating to children in the age group of interest to this report. Limitations (from the authors) - Included studies had short follow-up durations, thus the impact of fortified milk or cereal food on functional health outcomes could not be assessed thoroughly. - Pooled estimates have to be interpreted cautiously as statistical heterogeneity between studies was considerable. Possible sources for unexplained heterogeneity might be underreporting for co-interventions or the diversity of

Study	Methods	Included studies	Results	Comments
	- Measure of morbidity (for example, disease rates) or mortality Statistical analyses - Random effects model - Heterogeneity: I^2 statistic - Prespecified subgroup analyses: fortified milk compared with cereal foods, HIC compared with LMIC, single compared with dual compared with multiple micronutrient fortification. - Meta-regression analysis performed to evaluate the unique contribution of other independent factors (chosen a priori) on the most often reported outcome (dependent variable: Hb level; independent variables: Hb levels before intervention; daily amount of fortified micronutrient; length of follow-up; completeness of follow-up).	example, medical or care centres, low income risk groups). - Follow-up periods were generally short and did not exceed one year (for all studies included in the SR, mean follow up: 8.2 months; range: 2.3 to 12). - Fortified milk was prepared with centrally-processed fortified milk powder in most of the studies. Fortified cereals comprised centrally-processed complementary baby food, such as fortified porridge, gruel or weaning rusk to prepare a pap.		applied preparations that have influence on micronutrient absorption. Limitations (from the review team) - Findings were not stratified by baseline nutritional status - Publication bias not investigated. AMSTAR 2 overall confidence rating: low
Hojsak et al (2018) 'Young Child Formula: A Position Paper by the ESPGHAN Committee on Nutrition' Funding None specified Declaration of interest Various authors declared that they received funding from industry (Nestle, Danone, Nutricia)	Research question To review the composition of young child formula (YCF) and consider their role in the diet of young children Search criteria *Search dates:* up to January 2017 *Study design:* human studies *Population:* children aged 0 to18 years *Intervention or exposure and comparators:* YCF Primary outcomes Outcomes were determined that may identify any possible beneficial effect of YCF, and to review available data on the composition of YCF.	Number of studies 19 studies (7 RCTs, 1 cluster-RCT, 10 CS and 1 simulation study), of which 17 included participants aged 12 to 60 months at baseline. Of these, 3 RCTs and 1 cluster-RCT (reported in 6 publications) examined the association between YCF and health. Two RCTs that examined the effect of YCF on iron status were included in more comprehensive SRs included in this report. Their findings on iron status have not been extracted under this SR.	Results of interest for the age group covered in this report Vitamin D status (3 RCTs) All 3 studies reported that vitamin D-fortified YCF improved vitamin D status (See Annex 9, Table A9.22 for details). Blood zinc concentrations (1 RCT) The RCT reported no differences in serum zinc concentrations among children randomised to receive YCF fortified with zinc and other micronutrients, red meat or nonfortified cows' milk Immunoglobulin A (IgA) (1 cluster-RCT) The cluster-RCT reported an increase in IgA with YCF supplemented with synbiotics (*Lactobacillus paracasei* NCC2461	Risk of bias or quality Quality assessment of studies was not performed. Confounding factors No mention of confounding factors or adjustment for these Limitations (from the authors) None reported Limitations (from the review team) - Literature search not comprehensive for vitamin D as an exposure or intervention - Publication bias not assessed - 2 of the 5 studies of interest reported on the same RCT

Study	Methods	Included studies	Results	Comments
		Countries Mostly high income countries (HIC) Outcomes Outcomes of interest to this report: vitamin D status, zinc status, serum IgA	and *Bifidobacterium longum* NCC3001; inulin and fructo-oligosaccharides) and vitamins (A, C, and E), minerals (zinc and selenium), and docosahexaenoic acid compared with regular YCF. The study was funded by Nestle.	- Findings were not stratified by baseline nutritional status AMSTAR 2 overall confidence rating: critically low
Imdad et al (2017) 'Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age' Funding The WHO Declaration of interest The authors alone are responsible for the opinions and views expressed in this publication. Imdad was paid for writing this review by the WHO. Evan Mayo-Wilson - none known. Bhutta's institution received a grant from the WHO for this review and two additional vitamin A related Cochrane reviews (Imdad 2016; Haider 2017). Bhutta is an Editor for Cochrane Developmental,	Research question To assess the effect of vitamin A supplementation (VAS) compared to placebo or no intervention for preventing morbidity and mortality in children aged 6 months to 5 years. Search criteria *Search dates:* up to March 2016 *Study design:* RCTs and cluster-RCTs *Population*: children aged 6 months to 5 years; hospitalised children and children with disease or infections were excluded. *Intervention and comparators:* synthetic VAS compared to placebo or treatment-as-usual control group, including various doses and frequencies; co-interventions must have been identical in both groups to be included; food fortification, consumption of foods rich in vitamin A, and beta-carotene supplementation were excluded. Primary outcome All-cause mortality (not of interest to this report)	Number of studies 47 RCTs (42 included in MAs) Number of participants Total n=1,223,856 Studies ranged from 35 participants to over 1 million. Age of participants All studies were on participants aged 6 months to 5 years. 21 (44%) studies reported average age, which was 33 months across the studies. Countries Low income countries (LIC), lower middle income countries (LMIC) and upper middle income countries (UMIC) Intervention All studies used large doses of vitamin A in the range of 50,000 International Units (IU) to	Results of interest to this report Vitamin A deficiency (4 trials; 2262 participants; mean follow-up: 54.5 weeks) - RR 0.71; 95% CI 0.65 to 0.78; I^2=78% (GRADE: moderate) Vitamin A serum retinol levels at follow-up (14 trials) - SMD 0.26; 95% CI 0.22 to 0.30; I^2=95% - Random-effects model: SMD 0.50; 95% CI 0.30 to 0.70 - Funnel plot highly asymmetrical Bitot's spots - incidence (1 trial): no effect reported (RR 0.93; 95% CI 0.76 to 1.14) - prevalence (5 trials; 1,063,278 participants; mean follow-up: 80.72 weeks): RR 0.42; 95% CI 0.33 to 0.53; I^2=49% (GRADE: moderate) Night blindness - incidence (1 trial): RR 0.53; 95% CI 0.28 to 0.99 - prevalence (2 trials; 22,972 participants; follow-up: 52 to 68 weeks): RR 0.32; 95% CI 0.21 to 0.50; I^2=0% (GRADE: moderate) Xerophthalmia - incidence (3 trials): not significant	Risk of bias or quality - Risk of bias assessed using Cochrane's tool. - Quality of evidence for primary outcome (GRADE): high. Confounding factors - Authors noted that the magnitude of the effect may differ across settings and populations (possibly due to the extent of VAD), concomitant nutrient deficiencies may impair bioavailability of the supplements, and comorbid illnesses may reduce absorption of vitamin A. Limitations (from the authors) - The authors combined risk ratios (events per child) and rate ratios (events per child-year) for incidence data but noted that this was not ideal. - Subgroup analyses were vulnerable to reporting bias (differences more likely to be reported than similarities). -Secondary analyses were more likely to be influenced by missing data than primary outcome.

Study	Methods	Included studies	Results	Comments
Psychosocial and Learning Problems.	<u>Secondary outcomes</u> Of interest to this report - Bitot's spots, night blindness, xerophthalmia - Vitamin A deficiency (VAD) status <u>Statistical analyses</u> - Fixed-effects model - Heterogeneity (visual inspection of forest plots, Chi^2 test and I^2 statistic) deemed to be substantial if Chi^2 $p<0.10$ and $I^2> 50\%$. - Subgroup analyses (dose, frequency, geographical location, sex, age (6 to 12 months compared with 1 to 5 years) - Sensitivity analyses: • test for bias (for studies at high risk of bias for sequence generation) • small study bias using random-effects model and funnel plots (for outcomes with ≥10 outcomes) • robustness of results when using imputed intracluster correlation coefficients.	200,000 IU (1 IU = 0.3mcg), depending on the age of participants, except for 5 studies that used smaller doses (3866 to 25,000 IU). Participants received the large doses (50,000 IU to 200,000 IU) every 4 to 6 months, either once or more, depending on the study duration. Studies that used smaller doses gave more frequent doses. <u>Intervention duration</u> 5 studies continued for 5 years or more, the remainder of the studies lasted about 1 year or less.	- prevalence (2 studies): RR 0.31 (95% CI 0.22 to 0.45; I^2=0%). See Annex 9, Tables A9.17 and A9.19 for more details.	- Out of 47 studies, 20 excluded children with VAD but vitamin A status was unclear in 23. - A general weakness of many of the included interventions was the under-reporting of implementation data, such as the core components of an intervention, the degree to which they are delivered in practice, and what aspects of the trial may have influenced implementation. - Findings were not stratified by baseline nutritional status <u>AMSTAR 2 overall confidence rating:</u> high
Matsuyama et al (2017) 'Effect of fortified milk on growth and nutritional status in young children: a systematic review and meta-analysis' <u>Funding</u> No specific grant from any funding agency in	<u>Research question</u> To assess the effect of fortified milk on growth and nutritional status in young children <u>Search criteria</u> *Search dates:* to June 2014 *Study design:* RCTs of minimum 4 months duration *Population:* healthy children aged 6 to 47 months	<u>Number of studies</u> 15 publications (reporting on 12 RCTs). Of these, 10 publications (7 RCTs) included participants aged 12 to 60 months. To note 1 RCT was included in most of the SRs identified on iron. <u>Intervention</u> - Duration ranged from 5 to 12 months.	<u>Results of interest to this report</u> Iron biomarkers See Annex 9, Table A9.11 for detailed results on Hb, serum ferritin, anaemia, including subgroup analyses for anaemia in children aged >12 months at baseline (only outcome for which subgroup analyses were reported in the SR). Other Fe status outcomes (not extracted in detail in Annex 9) - Body iron (1 study): higher in multiple micronutrient (MMN)	<u>Risk of bias or quality</u> - Risk of bias assessed using Cochrane tool. - Funnel plot for anaemia showed symmetry, suggesting minimal publication bias. - Certainty of evidence not graded. <u>Confounding factors</u> Most studies reported any baseline imbalance between groups (number of participants

Study	Methods	Included studies	Results	Comments
the public, commercial or not-for-profit sectors. One author is partially funded by Danone Nutricia. Declarations of interest None to declare	*Intervention:* fortified milk or formula with micronutrients or prebiotics, probiotics or synbiotics, or had modified macronutrient content *Comparators:* Non- (or low-) fortified milk or formula. Primary outcomes - Body size (for example, weight, height or length, BMI, head circumference) - body composition - biochemical markers Statistical analyses - MA conducted for the age group 6 to 47 months. - Random-effects model used for studies with I^2>0·40. - Risk of bias assessed through funnel plot. - Subgroup analyses: study country's economic status, the intervention duration and the age of participants.	- Most common fortificants (of interest to this report): Fe and vitamin C, followed by Zn, vitamin D - Other fortificants: long chain polyunsaturated fatty acids (LC-PUFA) and prebiotics, probiotics or synbiotics. - Control milk varied from standard cows' milk to no- or low-fortified 'follow-on-formula'. Countries High income countries (HIC), lower middle income countries (LMIC) and upper middle income countries (UMIC)	intervention group compared with control - Zinc protoporphyrin, haematocrit and red-cell distribution (1 study): improvement reported in MMN intervention group compared with control - Mean corpuscular volume (2 studies): improvement in 1 study (UK, MMN fortification), no difference in the other (Sweden, dual fortification with iron + vitamin C) Serum zinc (5 RCTs) - Zn fortified milk did not result in significant change in serum Zn concentration in any of the studies. Body size outcomes Findings not extracted because trials tested milk fortified with LC-PUFA or prebiotics or synbiotics	between groups, potential baseline imbalances) but none were deemed sufficiently extreme to have impacted the study outcome significantly. Limitations (from the authors) The operational definition of anaemia was not uniform, but mostly based on Hb concentration of <110 g/l. Limitations (from the review team) - Results that were not statistically significant were not reported. - Findings not stratified by baseline nutritional status - Subgroup analyses only reported for body size outcomes and anaemia AMSTAR 2 overall confidence rating: moderate
Mayo-Wilson et al (2014b) 'Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age' Funding Aga Khan University (Pakistan) and the Centre for Evidence-Based Intervention (UK).	Research question To assess the effects of zinc supplementation for preventing mortality and morbidity, and for promoting growth, in children aged 6 months to 12 years old. Search criteria *Search dates:* up to January 2013 *Study design:* RCTs and cluster-RCTs with a parallel group design; quai-RCTs excluded *Population*: children aged 6 months to 12 years at baseline; hospitalised children and children with chronic	Number of studies 80 RCTs, of which about 50 had participants aged 12 to 60 months. Most of the participants in the review were under 5 years of age; the median of the reported mean age was 28 months. Countries 73 (91%) studies were conducted in lower middle income countries mainly in Asia and Latin America. Intervention	Results of interest to this report Zinc versus no zinc See Annex 9, Table A9.16 for detailed results of main MA and subgroup MA in children aged 1 to <5 years for the following: - Growth (height, weight, weight-to-height ratio) - Blood zinc concentration - Risk of zinc deficiency - Blood Hb and ferritin concentrations - Prevalence of anaemia and iron deficiency Zinc plus iron versus zinc alone Findings for this comparison were not stratified by age group and	Risk of bias or quality - Risk of bias assessed using Cochrane tool. - GRADE used to assess certainty of evidence for primary outcomes - No publication bias detected for primary outcomes (funnel plots) Confounding factors - The authors did not comment on confounding factors (review of RCTs). However, they did comment on factors that might impact the effectiveness of zinc supplementation, such as meat intake, level of undernutrition, levels of fibre and phytate

Study	Methods	Included studies	Results	Comments
Declaration of interest 2 authors (Imdad and Bhutta) have published previous reviews on zinc; 1 author (Bhutta) was involved in some of the trials included in this review but has not participated to the data extraction of these trials. (Mayo-Wilson et al, 2014a), identified through the literature search, reported on the same systematic review and has therefore not been extracted into evidence table.	diseases or with conditions that could affect growth were excluded *Intervention and comparators:* preventive oral zinc supplementation compared with no intervention, a placebo or a waiting list control; food fortification or intake, sprinkles, and therapeutic interventions excluded; co-interventions were included if the same co-intervention were administrated to both groups; comparisons of iron + zinc versus zinc alone were also included in order to evaluate the effect of providing zinc and iron simultaneously. Primary outcomes - All-cause mortality and cause-specific mortality due to all cause diarrhoea, LRTI and malaria (not of interest to this report) Secondary outcomes of interest to this report: growth, micronutrient status and adverse events. Statistical analyses - Fixed-effects model - Heterogeneity (visual inspection forest plots, Chi^2 test and I^2 statistic) deemed to be substantial if Chi^2 $p<0.10$ and $I^2> 50\%$ - Subgroup analysis conducted for outcomes with ≥10 studies, including country income level, age (6 to <12 months compared with 1 to <5 years compared with 5<13 years) dose and iron co-intervention. - Planned sensitivity analyses: • random-effects model	- Studies for which the formulation of zinc was reported: zinc was provided as a solution or syrup (46), pill or tablet (17), capsule (6), or powder (2). - Studies reporting the chemical compound of their zinc supplements provided zinc as sulfate (45), gluconate (12), acetate (6), and other compounds (8). - Studies provided zinc for <2 months (8), 2 to <6 months (22), 6 to <12 months (33), and ≥12 months (16). - Zinc was provided daily in 48 studies and 11 provided zinc weekly. - Studies that could be classified based on zinc dose administered daily dose equivalents of <5 mg (5), 5 mg to <10 mg (19), 10 mg to <15 mg (30), 15 mg to <20 mg (8), and ≥20 mg (12). - 20 trials were factorial. Among both factorial and non-factorial trials, there were 100 eligible comparisons. Of these eligible comparisons, 51 (49%) included a co-intervention that both the zinc and the control groups received. Common co-interventions were iron,	therefore are not specific to children aged 1 to 5 years. See Annex 9, Table A9.16 for results for the following: - Growth (height, weight, weight-to-height ratio) - Zinc status - Iron status	consumption, disease prevalence and pathogen profiles. Limitations (from the authors) - As most of the studies were conducted in LMIC, results might not be applicable to HIC. - Studies of zinc with an iron co-intervention versus those without were analysed, but the review was not primarily designed to explore this relationship fully. - The authors noted that the evidence for secondary outcomes and adverse events was more mixed, that heterogeneity was significant for some of these outcomes which remains largely unexplained and that they were more likely to be influenced by selective reporting. Limitations (from the review team) - Findings were not stratified by baseline nutritional status - Outcomes not directly relevant to UK population were not extracted, including the primary outcome 'mortality due to malaria' and the secondary outcomes related to malaria and stunting. - Only the subgroup analyses for age, iron co-intervention and country income level (where available) were extracted. - The authors did not conduct sensitivity analyses to assess the potential impact of risk of bias in individual studies on the results of the meta-analyses. AMSTAR 2 overall confidence rating: moderate

Study	Methods	Included studies	Results	Comments
	• test for bias (for studies at high risk of bias for sequence generation) – not performed • robustness of results when using imputed ICCs – not performed - Publication bias (funnel plots) assessed for MA with ≥10 studies	vitamin A, or multivitamin supplements.		
Pasricha et al (2013) 'Effect of daily iron supplementation on health in children aged 4-23 months: A systematic review and meta-analysis of randomised controlled trials' <u>Funding</u> Supported by grants from the Government of Victoria, the Royal Australasian College of Physicians and the University of Melbourne (Australia) <u>Declaration of interest</u> None to declare	<u>Research question</u> To comprehensively assess the effect of daily iron supplementation in children aged 4–23 months on important haematological and non-haematological outcomes and adverse effects. <u>Search criteria</u> *Search dates*: until February 2013 *Study design*: RCTs *Population*: healthy children aged 4 to 23 months (or at least 75% of participants within the designated age range) *Interventions and comparators*: daily oral iron supplements versus control; iron supplements combined with a second intervention included if co-intervention applied identically (without iron) in the control group <u>Primary outcomes</u> - Haemoglobin (g/l) - Anaemia (defined by study investigators) - Iron status (iron indices, including ferritin) - Iron deficiency, ID (defined by study investigators) - Iron deficiency anaemia, IDA (defined by study investigators) - Cognitive and psychomotor	<u>Number of studies</u> 35 studies (49 articles), of which 13 included participants aged 12 to 60 months (although not exclusively). The rest were in children aged up to 12 months. Only findings from MAs where the % weighting from studies that included children aged 12 to 60 months was >50% were extracted into Annex 9. If this information was not available, the data were extracted (see Immune function). <u>Countries</u> Mainly middle income countries <u>Interventions</u> - Most trials provided iron as ferrous salts, with daily doses typically of 10 to 15 mg or 3 to 6mg per kg, either alone, or with other micronutrients (mainly zinc, folic acid or vitamins A, C or D).	<u>Results of the SR (in children aged 4 to 23 months)</u> Cognitive development See Annex 9, Table A9.19 on mental development. Findings on psychomotor development were not extracted because <50% weighting in MA from studies in children aged 12 to 60 months Immune function See Annex 9, Table A9.20; to note that it was unclear from the SR or MA which studies contributed to the findings. Therefore, findings may relate to children < age 12 months. Iron status or haemotological parameters and growth outcomes Findings not extracted because <50% weighting in main MA were from studies in children aged 12 to 60 months Subgroup analyses for each outcome by dose, intervention duration, present breastfed status, and malaria endemicity not extracted. Posthoc analyses of iron intervention (alone	<u>Risk of bias or quality</u> - Risk of bias assessed using Cochrane - Sensitivity analysis performed with studies considered at low overall risk of bias - Funnel plots to assess potential publication bias <u>Confounding factors</u> The review authors did not comment on confounders. <u>Limitations</u> (from the authors) - The risk-benefit analysis on the effects of iron supplements on mental development in young children (needed for appropriate guideline development) is affected by the inability to definitively quantify cognitive benefits. - The conclusions on the effects of iron supplementation on growth in children who are anaemic or iron deficient are limited by the scarcity of data. <u>Limitations</u> (from the review team) The age group of interest for this SR was 4 to 23 months, without differentiating 4 to 12 months from 12 to 23 months.

Study	Methods	Included studies	Results	Comments
	development - Physical growth - Safety (that is, gastrointestinal effects, infections such as malaria, mortality). Meta-analysis - MA conducted for outcomes reported by at least 2 trials. - Random-effects model - For each outcome, subgroup analyses performed: baseline anaemia and iron status, dose and duration of supplementation, present breastfed status, and malaria endemicity. Posthoc analyses performed comparing iron compared with control and iron in combination with another nutrient compared with that nutrient alone. - Sensitivity analysis performed including only studies at low risk of bias. - Publication bias assessed with funnel plots for outcomes with more than 10 trials.	- Most interventions had a duration between 3 and 6 months.	or in combination with another nutrient) was also not extracted. Effect of iron on other micronutrients Findings not extracted because all studies included in MAs were in children aged <12 months at baseline.	AMSTAR 2 overall confidence rating: high
Pratt (2015) 'A review of the strategies used to reduce the prevalence of iron deficiency and iron deficiency anaemia in infants aged 6–36 months' Funding Not specified Declaration of interest The author is employed	Research question To compare the effectiveness of several strategies used to reduce the prevalence of ID and IDA in infants aged 6 to 36 months. Search criteria *Search dates*: from 2004 to October 2014 *Study design*: RCTs, quasi-randomised trials and non-randomised controlled trials *Population*: children aged 6 to 36 months at enrolment, either healthy or diagnosed with ID or IDA. All included	Number of studies 15 studies met the inclusion criteria, of which only 8 passed the quality assessment (see column 'comments'). Of the 8 studies, 5 included participants aged 12 to 60 months at baseline. 1 was included in the SR or MA by Matsuyama et al (2017). Number of participants Not specified. Sample size	Main results for the age group covered in this report See Annex 9, Table A9.11 for detailed results of the following strategies to improve iron status in young children. - Micronutrient sprinkles (1 trial) - Iron-fortified milk (3 trials) - Efficacy of different strategies (1 trial)	Risk of bias or quality Trial quality assessed using a modified CASP tool (11 criteria – details not provided). Each study was assigned a score out of 11. To pass the quality assessment, studies had to score ≥10. Confounding factors The review author did not comment on confounders. Limitations (from the author) - Review conducted by only 1 researcher (did not follow full SR protocol).

Study	Methods	Included studies	Results	Comments
by Nestle Nutrition UK and Ireland	studies were required to have a minimum of 30 subjects in total. *Interventions* and c*omparators*: types of interventions included any strategy or method used to reduce the prevalence of ID and IDA compared to control, or other current regiments to increase haemoglobin status and reduce the prevalence of ID and IDA Primary outcomes - Haemoglobin (g/l) - Anaemia (as defined by trialists) - Iron deficiency (ID) (as defined by trialists, based on biomarkers of iron status) - Iron status (as reported)	of 5 studies of interest ranged from 115 to 2283. Age of participants Of the 5 studies of interest, 3 studies had participants <12 months at baseline. Older children at baseline were 43 months (1 study). Older children at the end of interventions were aged 42 to 47 months (2 studies). Countries Mainly middle income countries Intervention doses - Typical supplementation dose was 12.5mg per day; typical dose in fortified milk was 5 to 6mg. - Average duration of the interventions was 6 months.		- In the quality assessment, points were deducted when participants were not blinded to the treatment. However, it remains almost impossible to conduct an intervention blind in nutrition science. Limitations (from the review team) - The search strategy stated that non-randomised controlled trials were included, but the PRISMA diagram stated that 3 studies were excluded because "assignment of patients to treatments not randomised" - IDA not listed as an outcome but in the research question - target group: 6 to 36 months, but in one place it says 3 to 36 months, and in the abstract 6 to 12 months - Not enough detail provided regarding quality assessment, including which studies failed the quality assessment and on which basis - Barely any discussion on baseline data and how this could have contributed to study heterogeneity. AMSTAR 2 overall confidence rating: critically low
Ramakrishnan et al (2009) 'Effects of micronutrients on growth of children under 5 years of age: meta-analyses of single	Research question To identify well-designed RCTs conducted in children <5 years old with selected micronutrients, both single and combined interventions, and conduct MA to evaluate the effect of	Number of studies Vitamin A: 17 studies Iron: 27 studies Zinc: 43 studies MM (≥3 micronutrients): 20 studies Number of participants	Main results (as reported in the SR) Vitamin A supplementation (see Annex 9, Table A9.21 for details) Vitamin A and zinc (2 studies): - height (0.10; 95% CI -0.41 to 0.61) - weight (0.11; 95% CI -0.58 to 0.80)	Risk of bias or quality - Study quality not assessed; publication bias was the only risk of bias taken into account by the review authors. - Absence of publication bias for most MAs, except for the effects of zinc on WHZ. Many studies that

Study	Methods	Included studies	Results	Comments
and multiple nutrient interventions" Funding Supported by the micronutrient initiative, Ottawa, Canada. Declaration of interest None to declare.	these interventions in improving child growth. Search criteria *Search dates:* up to April 2008 *Search design:* RCTs *Population*: children aged <5 years old *Intervention and comparators:* intervention provided to treatment and control children differed only in the inclusion of the micronutrients of interest (vitamin A, iron, zinc, or multiple micronutrients [MM]); studies with duration of follow-up <8 weeks, with lack of control groups or conducted on children with chronic diseases or conditions that affect growth were excluded. Primary outcomes - Annual change in height or height-for-age z-score - Annual change in weight or weight-for-age z-score - Annual change in weight-for-height z-score (WHZ) Statistical analyses - Random-effects model - Sensitivity analysis performed using different assumptions for the correlation between pre- and post-test variance. - Heterogeneity: chi square test of significance. - Subgroup analyses: mean initial age of children, duration of intervention, baseline nutritional status, baseline haemoglobin and, for MM	Vitamin A: sample size ranging from 51 to 21,250. For the other interventions, sample sizes were smaller, with a maximum of 407 for iron, 1665 for zinc and 386 for MM. Countries Mainly lower middle income countries (LMIC) Intervention Vitamin A: provided as a high dose supplement (60 mg) every 4 to 6 months in most studies; duration 12 to 104 weeks. Iron: delivered in the form of a tablet or syrup taken daily in most studies; most common dosage was 10 mg per day (higher doses of 20 to 60 mg per day used in some studies with children >15 months); duration 8 to 52 weeks. Zinc: mainly provided daily as a liquid supplement; dosage varied from 20mg per week to 20mg per day; duration 8 to 64 (median 24) weeks. MM: administrated as daily or weekly supplements (as foodlets, syrup or tablets) or fortified foods; 80% of the interventions contained vitamin A, iron and zinc.	- WHZ (0.05; 95% CI -0.12 to 0.22). Iron supplementation: findings were not extracted because <50% estimates (13 of 34) included in MA were from studies that included children aged 12 to 60 months. Zinc supplementation: findings were not extracted because <50% estimates (23 of 56) included in MA were from studies that included children aged 12 to 60 months. Iron and zinc, iron and folic acid: findings were not extracted because all studies in MA were in children aged <12 months. MM ≥ 3 micronutrients: findings were not extracted because <50% estimates (7 of 27) included in MA were from studies that included children aged 12 to 60 months.	reported effects of zinc on height and weight change did not report on WHZ, which may explain some of the observed publication bias. Confounding factors - No discussion included on confounding factors, although the review authors did perform subgroup analyses, including baseline nutritional status and baseline Hb. Limitations (from the authors) - The limited variability in the dosage used and lack of data on baseline nutrient status, especially zinc, made it difficult to identify the conditions under which these interventions might be beneficial. - Dearth of well-designed trials that evaluate the benefits of micronutrients in the context of food-based approaches or examine the long-term effects of these interventions. AMSTAR 2 overall confidence rating: critically low

Study	Methods	Included studies	Results	Comments
	interventions, mode of administration and combination of micronutrients. - Publication bias evaluated by the funnel plot, Egger's and Begg's tests.	Some also contained iodine (2 studies), selenium (4 studies) and copper (2 studies); duration 8 to 64 weeks.		
Thompson et al (2013) (Note that last author is Pasricha) 'Effects of daily iron supplementation in 2- to 5-year-old children: Systematic review and meta-analysis' <u>Funding</u> Victoria fellowship (Government of Victoria), a CRB Blackburn Scholarship (Royal Australasian College of Physicians) and an Overseas Research Experience Scholarship (University of Melbourne) <u>Declaration of interest</u> 1 author received an unrestricted research grant as a co-investigator from Vifor Pharma Ltd and has served as a consultant to the Meat and Livestock Authority Australia.	<u>Research question</u> To summarize the evidence for effects of daily iron supplementation administered to children aged 2 to 5 years of age. <u>Search criteria</u> *Search dates*: up to March 2012. *Study design*: randomized and quasi-randomized controlled trials *Population*: children aged 2 to 5 years, from all demographic and geographic settings; children with severe anaemia (Hb <70g/l) or suffering from a medical condition that substantially alters iron metabolism were excluded. *Interventions and comparators*: oral iron supplementation ≥5 days per week; oral iron supplement comprised iron salts and other compounds including carbonyl iron and colloidal iron; studies that included a co-intervention were included, provided that the co-intervention was also applied identically in the control arm. <u>Primary outcomes</u> - Hb concentration - Anaemia (defined by the authors) - Iron status (defined by iron indices) - Cognitive or school performance - Psychomotor performance - Physical growth - Safety <u>Meta-analysis</u> - Random-effects model	<u>Number of studies</u> 15 studies, all included participants aged 12 to 60 months at baseline. <u>Number of participants</u> Between 394 (cognitive development) and 1680 (Hb) participants contributed to the pooled estimates. <u>Countries</u> Mainly lower middle income countries (LMIC) <u>Interventions</u> - Most of the studies provided iron as ferrous sulfate, with daily doses between 10 and 82.5mg, either alone, or with other micronutrients (such folic acid or vitamins A or C, or zinc). - Most interventions had a duration between 1 and 12 months.	<u>Main results</u> Haematological measures For the following outcomes, see Annex 9, Table A9.12 for detailed results of main MA and subgroup MAs by baseline status (iron replete, iron deficient, anaemic, mixed, unknown or unreported status) - Haemoglobin - Ferritin - Anaemia No trials reported on iron deficiency or iron deficiency anaemia <u>Other haematologic parameters</u> No effect on transferrin saturation (MD 6.70%; 95% CI 1.68 to 11.72; p=0.74; I^2=0%; 3 studies), hematocrit (MD 0.00; 95% CI -0.01 to 0.01; p=0.66; I^2=25%; 3 studies) or mean cell volume (MD 2.49fl; 95% CI -1.10 to 6.08; p=0.17; I^2=70%; 2 studies). Physical growth See Annex 9, Table A9.14 for detailed results for weight or change in weight or weight z-scores; height or change in height or height z-scores Cognitive development Authors noted that 2 of 4 studies that examined this outcome had data that could be extracted. Both studies were in participants with mixed or	<u>Risk of bias or quality</u> - Risk of bias assessed using the Cochrane tool, which addresses selection, performance, attrition, detection, and reporting bias. - Studies were considered at low risk of bias if they were at low risk of both selection and allocation bias and one of detection, performance, or reporting bias. - All included studies were considered at high risk of bias. <u>Confounding factors</u> - Baseline characteristics of treatment and control groups were similar in all but one study. <u>Limitations</u> (from the authors) - There was a lack of studies measuring outcomes of anaemia, iron deficiency or iron deficiency anaemia. - Studies did not discuss or account for the effect of inflammation or infection on ferritin. - There were few data evaluating the impact of iron supplementation on development. - Only 4 outcomes contained sufficient trials to enable subgroup analysis. - Techniques such as meta-regression could not be used

Study	Methods	Included studies	Results	Comments
	- Clinical heterogeneity assessed by determining similarity between subjects and outcomes of included studies. Statistical heterogeneity determined using I^2 tests. - Subgroup analysis performed on outcomes containing > 3 studies. Subgroups included sex; baseline Hb, iron status; breastfeeding status; daily iron dose; duration of supplementation; and malaria endemicity of the setting. - Publication bias (funnel plot) could not be assessed because no outcomes contained more than 10 studies.		unknown baseline iron status. Findings from these 2 studies were therefore not extracted in Annex 9. Infection See Annex 9, Table A9.15 for detailed results	because of the paucity of the studies. AMSTAR 2 overall confidence rating: moderate

Foods, dietary patterns and dietary components

Table A5.3 Evidence table – foods, dietary patterns and dietary components

Study	Methods	Included studies	Results	Comments
Costa et al (2018) 'Consumption of ultra-processed foods and body fat during childhood and adolescence: a systematic review' Funding No specific grant support Declaration of interest None to declare	Research question To review the available literature on the association between consumption of ultra-processed foods and body fat during childhood and adolescence. Search criteria *Search dates:* up to 15 July 2016 *Study design:* human studies *Population:* healthy children and adolescents *Intervention or exposure and comparators:* consumption of ultra-processed food as defined by the NOVA food classification Primary outcomes Body fat	Number of studies 26 studies (5 trials, 15 PCS, 6 CS), of which 3 PCS had participants aged 12 to 60 months at baseline. Number of participants Of the 3 PCS of interest, n=292, 585 and 4750 Age of participants Participants were aged between 3 and under 5 years at baseline and followed up until age 8 years (1 study), 15 years (1 study) and 18 years (1 study) Countries High income countries	Results of interest for the age group covered in this report Of the 3 studies, 2 reported that dietary patterns consisting of processed foods were associated with increased body fat in both sexes and 1 study found the same association only in boys (see Annex 9, Table A9.25 for details).	Risk of bias or quality - STROBE used to evaluate observational studies (maximum score 22); CONSORT used to evaluate intervention studies (maximum score 25) - Quality score of the 3 studies of interest were not reported. AMSTAR 2 overall confidence rating: moderate

Study	Methods	Included studies	Results	Comments
de Beer (2012) 'Dairy products and physical stature: a systematic review and meta-analysis of controlled trials' Funding Not specified Declarations of interest Not specified	Research question Do dairy products supplementation trials in children or adolescents consistently show extra linear growth compared to the growth effect of usual diet? Search criteria *Search dates:* cut-off date not specified *Study design:* randomised and non-randomised controlled trials *Population:* children and adolescents (age 2 to 18 years); very low birth weight infants, participants with a history of diseases that negatively influenced physical growth, and overweight or obese participants were excluded. *Intervention and comparators:* supplementation of usual diet with dairy products Primary outcome Linear growth	Number of studies 12 trials (7 RCTs and 6 non-RCTs), of which 1 RCT included children aged 12 to 60 months at baseline. Number of participants The RCT of interest included 402 participants Age of participants Participants had a mean age of 3.3 years at baseline and the study had a 9-month duration Countries Upper middle income countries	Results of interest for the age group covered in this report The 1 RCT found that children randomised to receive yoghurt (125g) for 5 days a week experienced a greater change in height (cm) than children in the control group (no intervention) (see Annex 9, Table A9.24 for details).	Risk of bias or quality - Study quality assessed using an adaptation of a checklist developed by Tulder et al (2003) and Steultjens et al (2004). Confounding factors - Review mentions that in order to test the hypothesis that dairy products have a special effect on growth above and beyond its contribution to energy intake, controlling for energy intake in trials is necessary. The study of interest did not control for energy intake. - None of the included studies controlled for energy expenditure (physical activity). AMSTAR 2 overall confidence rating: critically low

Study	Methods	Included studies	Results	Comments
Delgado and Matijasevich (2013) 'Breastfeeding up to two years of age or beyond and its influence on child growth and development: a systematic review' Funding Not specified Declaration of interest Not specified	Research question (1) to describe the global prevalence of breastfeeding up to two years of age or beyond and the global trends in prevalence rates over the past three decades; and (2) to conduct a systematic literature review on the medium-term effects of breastfeeding up to two years of age or beyond on two crucial aspects of child health: growth and development. Search criteria *Search dates:* cut-off date not specified *Study design:* not specified *Population:* <18 years old *Exposure and comparators:* breastfeeding up to 2 years and beyond Primary outcomes Child growth and development	Number of studies 8 studies (4 PCS, 4 CS), of which 8 had participants aged 12 to 60 months at baseline (4 PCS, 4 CS). Number of participants Of the 4 PCS of interest, 1 had 2752 participants, 1 had 1979, 1 had 443 and 1 had 28,753. Age of participants All 4 PCS of interest included children breastfed to 24 months or beyond and followed up for between 6 months and 6.5 years. Countries Lower middle income countries (LMIC) and lower income countries (LIC)	Results of interest for the age group covered in this report Child growth (2 studies) Of the 2 studies, 1 found that children breastfed ≥2 years gained less weight between than those who were on solid foods only and 1 found that children breastfed ≥2 years had higher growth than children who had stopped breastfeeding Child development (2 studies) Of the 2 studies, neither found an association between continued breastfeeding and cognitive or psychosocial development (see Annex 9, Table A9.29 for details).	Risk of bias or quality - Study quality assessed using a modified Downs and Black scale which analyses 19 characteristics (including reporting, validity, bias, confounding and power of the study), with a maximum possible score of 20 points. - Of the 4 studies of interest, 1 scored 16, 1 scored 13, 1 scored 15 and 1 scored 17. AMSTAR 2 overall confidence rating: critically low

Study	Methods	Included studies	Results	Comments
Dougkas et al (2019) 'A critical review of the role of milk and other dairy products in the development of obesity in children and adolescents' Funding The Dairy Council Declarations of interest None to declare	Research question To review intakes of milk and other dairy products, and obesity and indicators of adiposity, in children. Search criteria *Search dates:* January 1990 to June 2017 *Study design:* cross-sectional, prospective longitudinal studies and intervention studies *Population:* healthy children age 1 to 18 years at baseline. *Intervention or exposure and comparators:* milk and any dairy product (calcium-containing foods including milk, cheese, yoghurt) Primary outcomes - Obesity - Indicators of adiposity (BMI, BMI standard deviation score, BMI z-score, % body fat, waist circumference, body weight status)	Number of studies 94 studies (31 PCS, 20 RCT, 43 CS) of which 14 PCS and 1 RCT included children aged 12 to 60 months at baseline. Number of participants Of the 15 studies of interest, sample sizes ranged from 49 to 14,224. Four studies included <100 participants; 4 studies included >100 to <500; 2 studies included >500 to <1000; 2 studies included >1000 to <5000; 3 studies included >5000 Age of participants Of the 15 studies of interest, all included children aged 1 to 5 years at baseline (with one study including children up to age 6 years). Follow-up duration ranged from 8 months to 12 years. Countries High income countries	Results of interest for the age group covered in this report Milk intake and later BMI or adiposity (4 studies) Of the 4 studies, 3 found no association and 1 found an inverse association. Low fat compared with full-fat dairy product intake and later BMI or adiposity (2 studies) Results from the 2 studies were inconsistent. Other dairy foods and later BMI or adiposity (1 study) found direct association between lower cream or crème fraiche intake and overweight or obesity Total dairy intake and later BMI or adiposity (4 publications reporting on 2 PCS) Of the 4 studies, 3 that reported adjusted analyses reported an inverse association. Nutrients consumed from dairy products and later BMI or adiposity (2 studies) One of the 2 studies found that higher total dairy protein intake per day was associated with an increase in weight The second study found that greater increases in energy consumed from milk were inversely associated with changes in children's waist circumference. (See Annex 9, Tables A9.24 and A9.30 for details)	Risk of bias or quality Study quality was not assessed. Limitations (from the review authors) - High variation on the definition and inclusion of dairy foods and type of milks, and definition and reporting of dairy food serving sizes - Variation in reporting of outcome variables related to weight status and adiposity measures - Lack of regular assessment of dairy product and dietary intake throughout childhood and adolescence in the included studies. The patterns regarding the type of milk and other dairy product consumption might not be stable over time especially given the introduction and greater availability of reduced-fat dairy products over the last 25 years - Adjustment for important confounding factors were inconsistent and varied among the studies, making it difficult to interpret and compare the results across study cohorts - One-third of the 31 PCS included in the review were funded by the dairy or private industry; 5 of 10 industry- or privately-funded studies showed favourable results for dairy foods compared with 4 of 21 publicly-funded studies

Study	Methods	Included studies	Results	Comments
				AMSTAR 2 overall confidence rating: low
Dror and Allen (2014) 'Dairy product intake in children and adolescents in developed countries: trends, nutritional contribution, and a review of association with health outcomes' Funding International Dairy Federation Declarations of interest None to declare	Research question To evaluate milk and dairy product intake among children and adolescents in developed countries and to consider how dairy product consumption is related to key nutrient intake and health outcomes. Search criteria *Search dates:* to September 2012 *Study design:* cross sectional, cohort, case-control and intervention trials (controlled and not controlled) *Population:* healthy children aged 2 to 19 at baseline *Intervention or exposure and comparators:* dietary milk or dairy intake Primary outcomes - Adiposity - Bone mineralization (studies reporting only bone mineral density rather than bone mineral content were excluded on the basis of dynamic bone turnover in children) - Dental health - Linear growth - Blood pressure	Number of studies 78 studies, of which 9 PCS included children aged 12 to 60 months at baseline. Of the 9, 1 of these studies (Rangan et al 2012) reported on 3 outcomes (BMI or body fat or energy balance, linear growth and blood pressure). Number of participants Of the 9 studies of interest, sample sizes ranged from 53 to 1,345. Three studies included <100 participants; 4 studies included >100 to <500; 1 study included >500 to <1000; 1 study included >1000 to <5000. Age of participants Of the 9 studies of interest, all included children aged 1 to 5 years at baseline (with two study including children up to age 6 years). Follow-up duration ranged from 8 months to 16 years. Countries High income countries	Results of interest for the age group covered in this report BMI, body fat or energy balance (5 studies) All 5 PCS (Rangan et al 2012, Moore et al 2006, Huh et al 2010, Newby et al 2004, Carruth and Skinner 2001) were included in the review by Dougkas et al 2019. See Annex 9, Table A9.24 for details of these studies. Bone health (1 study) - 1 PCS found that ≥2 servings per day of dairy through childhood was associated with bone health Linear growth (1 study) - 1 PCS found no association between height and dairy consumption (See Annex 9, Table A9.24 for details) Blood pressure (2 studies) Both studies found an inverse association between dairy intake in early childhood and lower blood pressure in middle childhood to early adolescence. (See Annex 9, Table A9.24 for details) Dental health (1 study) - 1 PCS found that median milk intakes at age 2 and 3 years was lower in children with caries (See Annex 9, Table A9.46 for details).	Risk of bias or quality Study quality was not assessed. Limitations (from the authors) - Few studies have measured biomarkers of nutrient status associated with dairy consumption in children - Aspects of the metabolic syndrome, which have been inversely associated with dairy intake in animal models and adults, warrant research in children and adolescents AMSTAR 2 overall confidence rating: critically low

Study	Methods	Included studies	Results	Comments
Karalexi et al (2018) 'Non-Nutritive Sweeteners and Metabolic health Outcomes in Children: A Systematic Review and Meta-Analysis' Funding Not stated. The authors are from the Third Department of Pediatrics, National and Kapodistrian University of Athens, General University Hospital "Attikon", Athens, Greece Declaration of interest None to declare	Research question to systematically identify, critically appraise, and quantitatively synthesize current evidence regarding the potential association of non-nutritive sweeteners (NNS) consumption during childhood and adolescence with negative metabolic outcomes, including obesity and diabetes. Search criteria *Search dates* up to 12 February 2017 *Study design:* cohort and case control studies *Population*: Children under 18 years of age *Exposure and comparators:* consumption of non-nutritive sweeteners (assessed by validated food frequency questionnaires with record period varying from 24h to 30 days) Primary outcomes Risk of obesity and diabetes	Number of studies 13 PCS of which 3 had participants aged 12 to 60 months at baseline. Number of participants The 3 PCS of interest included n=177, 1345, 2547 participants Age of participants Participants were aged 2 to 4.5 years at baseline and followed up for 6 months to 10 years Countries High income countries	Results of interest for the age group covered in this report Change in BMI or BMI z-score (2 studies) Both studies found no association Diabetes (Type 1) (1 study) 1 PCS in children at increased risk of developing type 1 diabetes (T1D) found no association (See Annex 9, Table A9.28 for details for both outcomes) Review's conclusion Comprehensive assessment of existing literature provides inconclusive evidence regarding the impact of NNS intake in childhood on metabolic health.	Risk of bias or quality - Newcastle-Ottawa Scale used to score the quality of the studies - Factors that mainly compromised study quality were the unadjusted effect estimates and incompleteness of follow-up >80% of completeness - No evidence for publication bias (p=0.9) for the studies included in metanalysis Limitations (from the authors) - Data availability of the eligible studies, heterogeneity of methodological approaches in primary studies, NNS represent a rather heterogeneous class of items, self-reported data on the consumption of NNS, nonresponse from contacted authors AMSTAR 2 overall confidence rating: critically low

Study	Methods	Included studies	Results	Comments
Ledoux et al (2011) 'Relationship of fruit and vegetable intake with adiposity: a systematic review' Funding Robert Wood Johnson Foundation and federal fund from the USDA Agricultural Research Service children's Nutrition Research Centre Declaration of interest None to declare	Research question To assess the fruit and vegetable consumption to adiposity relationship Search criteria *Search dates:* 1980 to January 2009 *Study design:* longitudinal or experimental designs *Population*: healthy children, adolescents or adults *Intervention or exposure and comparators:* Intake of whole fruit and vegetables Primary outcomes Obesity and body weight	Number of studies 23 studies (12 experimental, 11 PCS), of which 2 PCS had participants aged 12 to 60 months at baseline Number of participants Of the 2 PCS of interest, n=971 and 1379 Age of participants Participants were aged 1 to 5 years at baseline and followed up for 6 months to 2 years Countries HIC Exposures Fruit and vegetables and intake was measured using an FFQ	Results of interest for the age group covered in this report Association between vegetables and fruit consumption and adiposity (2 studies) Of the 2 PCS of interest, 1 reported no association between vegetables and fruit consumption and adiposity and one found an association between greater vegetable consumption and adiposity. (See Annex 9, Table A9.23 for details) Review's conclusion The relationship of vegetables and fruit intake and adiposity among children remains unclear.	Risk of bias or quality - Research findings and their validity were compared by critiquing research methods. Research factors determined to enhance study validity included: rigor of study design, validity of measures, statistical adjustment of potential confounding variables (including dietary reporting bias), and sufficient sample size to detect hypothesized relationships. - The review included a rationale for assessing validity by specific indicators of research methods mentioned above but did not report on the outcomes of this assessment. - Studies were also assessed on how foods were classified as fruit or vegetable, whether adjustments were made for over- or under-reporting of dietary intake, how outcomes were measured (including by self-report or by trained personnel) - The 2 studies of interest did not control for energy expenditure and had only 3 years or less of follow up. AMSTAR 2 overall confidence rating: critically low

Study	Methods	Included studies	Results	Comments
Onubi et al (2015) 'Effects of probiotics on child growth: a systematic review' Funding Not specified Declaration of interest None to declare	Research question To add to the evidence of the effects of probiotics on child growth irrespective of age, type of probiotic bacteria or nutritional status of the children Search criteria *Search dates:* 1947 to October 2012 *Study design:* all study designs *Population*: well-nourished and under-nourished children; studies that looked at probiotic use for the management of a disease condition other than under-nutrition, and studies in children with impaired growth at birth were excluded. *Intervention and comparators:* probiotic product use (probiotic use for the management of a disease was excluded) Primary outcomes Change in weight, length or height, head circumference, BMI, mortality rate	Number of studies 12 studies (10 RCTs, 2 non-randomised clinical controlled trials), of which 2 RCTs were in well-nourished children aged 12 to 60 months and 4 studies were in under-nourished children aged 12 to 60 months. For the purposes of this RA, only results from the 2 studies in well-nourished children have been extracted. Countries High income countries and upper middle income countries Intervention The intervention in both studies of interest were multiple probiotics	Results of interest for the age group covered in this report Body weight or height gain (2 studies) One of the 2 studies found an effect and the second study found no effect (see Annex 9, Table A9.27 for details) Review's conclusion No evidence was found for a benefit of dietary intake of probiotics on growth in well-nourished children in developed countries. Some benefit was shown in terms of weight gain in the one study in well-nourished children in a developing country	Risk of bias or quality - Study quality assessed using a modified Cochrane review quality assessment form. - Both studies of interest had unclear risk of bias for allocation concealment AMSTAR 2 overall confidence rating: low

Study	Methods	Included studies	Results	Comments
Tandon et al (2016) 'The relationship between physical activity and diet and young children's cognitive development: A systematic review' Funding Supported by the Robert Wood Johnson Foundation's Healthy Eating Research Program Declaration of interest Not specified	Research question To systematically review the literature on the relationship between physical activity and dietary patterns and cognitive development in early childhood. *To note that the search and results are separated into 2 parts, here we only report on dietary patterns.* Search criteria *Search dates:* 2005 up to February 2016 *Study design:* all designs (except case studies) *Population:* children aged 6 months to 5 years at initial assessment *Intervention or exposure and comparators:* quantitative method of assessing total diet (for example, diet diary, 24-hour recall, food frequency questionnaire), dietary pattern, diet index score, meal composition or other indicator of overall diet quality; studies focusing solely on the effect of breastfeeding or breast milk were excluded. Primary outcomes Cognitive development	Number of studies 8 publications included on diet, of which 6 (reporting on secondary analyses from 3 PCS) assessed exposure in children aged 12 to 60 months. To note that 4 of the 6 studies of interest analysed data from the same PCS (Avon Longitudinal Study of Parents and Children). Number of participants The number of participants in the studies of interest ranged from 1366 to 7652. Age of participants See results column. Countries High income countries, including the UK	Results of interest for the age group covered in this report Cognitive development (6 publications reporting on secondary analyses from 3 PCS) All 6 publications found an association between some dietary patterns and measures of cognitive development (See Annex 9, Table A9.24, A9.25, A9.26 and A9.32 for details) Authors' conclusion: Our review found preliminary evidence suggesting a direct association between healthy dietary patterns (defined as diets high in fruits, vegetables, whole grains) before the age of 5 and later childhood cognitive outcomes. Although the findings provide some indication of direct associations, the limitations of the work point towards the need for additional investigations in this area.	Risk of bias or quality No formal assessment of quality of selected studies but authors broadly addressed study strengths and weaknesses Limitations (from the authors) - Each study created its own, slightly varied, definition of 'healthy' and 'unhealthy' dietary patterns. 'Healthy' usually aligned with recommendations in which fruits, vegetables and whole grains were important while 'unhealthy' usually included energy dense foods with high sugar and fat content. - Several of the studies were from the same ALSPAC cohort and had limited data on different ethnic minority groups and incomplete data from some groups which may limit generalisability. - In many studies (including some studies of interest), there was a significant gap in the ages at which diet and cognition were assessed leading to increased likelihood that other factors may have influenced the cognitive outcomes observed. AMSTAR 2 overall confidence rating: critically low

Drinks

Table A5.4 Evidence table – drinks

Study	Methods	Included studies	Results	Comments
Frantsve-Hawley et al (2017) 'A systematic review of the association between consumption of sugar-containing beverages and excess weight gain among children under age 12' <u>Funding</u> Robert Wood Johnson Foundation <u>Declaration of interest</u> Not specified	<u>Research question</u> To evaluate the available evidence examining the longitudinal association between adiposity and the consumption of sugar-containing beverages (SCB) (including SSBs and 100% fruit juice), and between adiposity and the consumption of only 100% fruit juices among children under age 12. <u>Search criteria</u> *Search dates*: to 29 March 2016 *Study design*: PCS, RCT and CCT *Population*: children aged <12 years at baseline; children with chronic health conditions (for example, diabetes, asthma) were excluded *Intervention or exposure and comparators*: - caloric SCBs (which include all sugar-sweetened non-dairy beverages and 100% fruit juice) - 100% fruit juice only <u>Primary outcomes</u> - Change in total adiposity (measures: BMI z-scores (BMIz), BMI, % body fat, weight change, incidence of obesity, incidence of overweight, prevalence of obesity, prevalence of overweight) - Change in central adiposity (measures: waist circumference, weight to hip ratio).	<u>Number of studies</u> 38 studies (1 RCT, 3 CCT and 34 PCS), of which 13 PCS had participants aged 12 to 60 months at baseline. 4 of 13 used data from 2 cohorts. <u>Number of participants</u> Of the 13 PCS, 8 included more than 1000 participants. <u>Countries</u> High income countries	<u>Results for the age group covered in this report</u> Association between SCB and BMI, overweight or obesity (9 PCS) To note that 3 PCS (Dubois, 2007, Lim, 2009 and Welsh, 2005) were included in the MA by Te Morenga et al (2012) - 6 PCS reported a direct association and 3 PCS reported no association (see Annex 9, Table A9.32 for details) Association between SSB and central adiposity - No studies identified within the age range of interest in this report. Association between fruit juice and total adiposity (7 PCS) (this evidence is reported in the 'Foods, dietary patterns and dietary components' chapter) - 4 PCS reported a direct association, and 3 PCS reported no association (see Annex 9, Table A9.32 for details) Association between fruit juice and central adiposity - No studies identified within the age range of interest in this report	<u>Risk of bias or quality</u> - Critical Appraisal Skills Programme (CASP) used for cohort study risk of bias assessment. <u>Limitations (from the authors)</u> - Review included only the results of the main analysis from each study. Results of analyses that were further stratified by baseline weight were not included, and it is possible that SCB consumption may have greater impact on those with different weight and obesity status at baseline. <u>Limitations (from the review team)</u> - The authors reported as a limitation that "almost all included studies were retrospective". It is unclear what they refer to as most of the included studies are prospective studies that assessed beverage consumption at baseline and in some cases at follow-up. <u>AMSTAR 2 overall confidence rating</u>: moderate

Study	Methods	Included studies	Results	Comments
Luger et al (2017) 'Sugar-Sweetened Beverages and Weight Gain in Children and Adults: A Systematic Review from 2013 to 2015 and a Comparison with Previous Studies' Funding European Association for the Study of Obesity Healthy Hydration Working Group Declaration of interest None to declare	Research question Association between sugar-containing drinks and body weight and obesity Search criteria Search dates: up to July 2008 Study design: RCT and cohort Population: children and adults Intervention or exposure and comparators: sugar-containing drink consumption Primary outcomes Body weight, BMI, adiposity	Number of studies 30 studies, of which 10 were in adults (9 PCS and 1 RCTs) and 20 were in children (17 PCS and 3 RCTs). Of the 20 studies in children, 6 included participants aged 12 to 60 months at baseline. Of these, 2 PCS were uniquely identified and included in this SR (see Annex 6, Table A6.1 for mapping of primary studies) and have been extracted into Annex 9, Table A9.2. Number of participants For the 2 PCS of interest, 1 PCS included 67 participants and the other included 227 participants Age of participants For the 2 PCS of interest, participants were aged 1 to 2 years at baseline and follow up was 6 months and 13 years Countries High income countries and upper middle-income countries	Results of interest for the age group covered in this report Both PCS reported a direct association between SSB consumption and risk of obesity or body weight (see Annex 9, Table A9.32 for details)	Risk of bias or quality For PCS, the Newcastle Ottawa Scale was used for risk of bias assessment AMSTAR 2 overall confidence rating: low

Study	Methods	Included studies	Results	Comments
Perez-Morales et al (2013) 'Sugar-sweetened beverage intake before 6 years of age and weight or BMI status among older children; systematic review of prospective studies' Funding Not specified Declaration of interest Not specified	Research question To conduct a systematic review of prospective studies that examined the association between SSB intake before six years of age and later weight or BMI status among older children. Search criteria *Search dates:* 2001 to 2011 *Study design:* prospective cohort studies *Population*: children < 6 years old *Exposure and comparators:* intake of SSB, including soft drinks, soda, fruit drinks, sports drinks, sweetened iced tea, and lemonade Primary outcome Body weight, BMI, waist circumference	Number of studies 7 PCS, of which 1 PCS was uniquely identified by and included in this SR (see Annex 6, Table A6.1 for mapping of primary studies) Number of participants The PCS included 135 participants Age of participants Participants were aged 3 to 5 years at baseline and followed up for 3 years Countries High income countries	Results from the PCS uniquely identified by this SR The PCS reported that SSB consumption was directly associated with child waist circumference (see Annex 9, Table A9.32 for details).	Risk of bias or quality - No formal tool was used to assess risk of bias; the review authors only commented that 2 of the studies had less risk of bias than the others. AMSTAR 2 overall confidence rating: critically low

Study	Methods	Included studies	Results	Comments
Te Morenga et al (2012) 'Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies' Funding University of Otago, the Riddet Institute (New Zealand) and the WHO Declaration of interest University of Otago, The Riddet Institute and the WHO; no other interests to declare	Research question Does reducing or increasing intake of dietary sugars influence measures of body fatness in adults and children? Search criteria *Search dates:* until December 2011 *Study design:* RCTs (≥2 weeks' duration) and prospective cohort studies (≥1 year in duration). Trials of weight loss or confounded by additional medical lifestyle interventions were excluded. *Population*: adults and children free from acute illness, and those with diabetes or other non-communicable diseases in whom conditions were regarded as stable *Intervention or exposure and comparators:* intake of total sugars (sucrose, free sugars), a component of total sugar or sugar-containing foods or beverages Primary outcome Body fatness (at least one measure) Statistical analyses - Random effects model - Heterogeneity (Q test and I^2 statistic); a I^2 value >50% and p<0.05 was indicative of heterogeneity. - Publication bias (Egger's test and funnel plot) - Sensitivity and meta-regression analyses performed for RCTs only.	Number of studies 68 studies (30 trials, 38 PCS), of which 7 PCS had participants aged 12 to 60 months at baseline. Number of participants Of the 7 studies of interest, samples ranged from 72 to 10,904 participants, with the majority of PCS including between 200 and 500 participants. Age of participants All the 7 studies of interest included children aged 1 to 5 years at baseline, with follow-up duration between 1 and 6 years. Countries HIC Exposure Most of the 7 studies of interest reported sugar exposure as sugar intake from beverages (SSB and fruit juice).	Main results (as reported in the SR) Association between SSB consumption and body fatness (7 estimates from 5 PCS, of which 5 estimates from 4 PCS are in children aged <60 months at baseline) - Increased risk of overweight or obesity among groups with the highest intake of SSB compared with those with the lowest intake (OR 1.55; 95%CI 1.32 to 1.82; p<0.001; I^2=0). - GRADE: low as all the studies were PCS; there was no further downgrading due to biases. See Annex 9, Table A9.32 for details.	Risk of bias or quality - RCTs assessed using Cochrane criteria and additional review-specific criteria including similarity, or not, of type and intensity of intervention in both arms, and whether studies were funded by industries with potentially vested interests. - GRADE assessment of the quality of evidence - Insufficient studies in children to investigate publication bias. - Unclear which methods were used to assess the quality of cohort studies. AMSTAR 2 overall confidence rating: moderate

Eating and feeding behaviours

Table A5.5 Evidence table – eating and feeding behaviour

Study	Methods	Included studies	Results	Comments
Appleton et al (2018) 'Sweet taste exposure and the subsequent acceptance and preference for sweet taste in the diet: systematic review of the published literature' Funding Unilever RandD Declaration of interests 3 authors had no DOI 2 authors were employees of Unilever	Research question Does dietary exposure to sweetness in humans impact on the generalised acceptance, preference, choice, and/or intake of sweet taste in the diet? Search criteria *Search dates*: until 15 August 2017 *Study design:* all studies testing relations of variation in exposure to sweetness and subsequent variation in acceptance, preference or choice of sweetened foods or beverages in humans aged >6 months. CS studies excluded. *Population:* children aged >6 months *Interventions or exposures*: exposure to or a manipulation of sweet taste through foods and beverages in the diet (for example, sugar-rich foods, low energy sweetener-sweetened foods or beverages, fruit). Studies required to include repeat (>1) taste exposure and a comparator group. Primary outcome Validated measure of perception (intensity), generalised acceptance, preference, choice	Number of studies 14 controlled trials (of which 2 were in children <6 years); 7 PCS (of which 2 were in children aged 12 to 60 months at baseline) Number of participants Of the 4 studies of interest, n=39 and 53 (controlled trials); n=493 and 1163 (PCS) Age of participants Age range 12 to 84 months (controlled trials) and 1 to 7 years (PCS) Countries High income countries	Results of interest for the age group covered in this report Controlled trials (2 studies): Both studies of interest manipulated exposure to sweet foods in the shorter-term (see Annex 9, Table A9.35 for detailed results) PCS (2 studies): Both PCS reported an association between exposure to juice or SSBs or confectionary and higher intakes in later years (See Annex 9, Table A9.35 for details) Author conclusions The available evidence does not provide clear, consistent support for a relationship between sweet taste exposures and the outcomes considered. Shorter term interventions suggested possible reduced preferences for sweet taste following greater exposure to sweetened stimuli, but findings from cohort studies and longer-term intervention trials were limited and equivocal.	Risk of bias or quality Risk of bias was rated using 4 domains: adequate study power; discrepancy between number of participants that enter the study (intention-to-treat population) and number included in analysis (intention-to-treat analysis); number of drop outs; incomplete outcome reporting. AMSTAR 2 overall confidence rating: moderate

Study	Methods	Included studies	Results	Comments
	and or intake of all or other sweet foods and beverages in humans aged >6 months.			
Bergmeier et al (2015) 'Systematic research review of observational approaches used to evaluate mother-child mealtime interactions during preschool years' Funding None to declare Declarations of interest None to declare	Research question What do findings reveal about the associations between observed mother-child mealtime interactions and preschoolers' eating and weight status? Search criteria *Search dates:* Jan 1925 to March 2014 *Study design:* studies in which mother-child mealtime behaviours were measured through observation *Population:* healthy children aged 2 to 6 years *Exposure and comparators:* observational measures of children's eating or mealtimes with mothers present (observed or self-reported) Primary outcomes - Children's eating behaviours or cognition - Maternal feeding practices or behaviours - Child weight status	Number of studies 13 studies (12 CS, 1 PCS). The PCS included participants aged 12 to 60 months at baseline. Number of participants The PCS of interest included 1218 participants Age of participants Participants were aged 15 months at baseline and followed up until age 36 months Countries High income countries	Results of interest for the age group covered in this report Maternal feeding behaviours and child weight status (1 PCS) The PCS reported that maternal assertive prompting and intrusive style had a small but significant association with greater child adiposity (BMI z-scores) at 36 months of age. See Annex 9, Table A9.37 for details. Review's conclusion about this study: the study highlighted that the type of prompt (for example, assertive prompt) rather than simply the total number of prompts was associated with greater child adiposity. Children's eating behaviours or cognition or maternal feeding practices or behaviours No studies in children aged 12 to 60 months were identified	Risk of bias or quality No formal quality assessment Limitations (from the authors) - None of the studies (including the PCS of interest) identified for the review evaluated how mutual dimensions (for example, parent responsiveness to the child and child responsiveness to the parent) of dyadic interactions between mothers and children influence maternal feeding practices, children's eating and weight. AMSTAR 2 overall confidence rating: critically low

Study	Methods	Included studies	Results	Comments
Blondin et al (2016) 'Breakfast consumption and adiposity among children and adolescents: an updated review of the literature' Funding None reported Declarations of interest None to declare	Research question What is the relationship between breakfast and adiposity in children? Search criteria *Search dates:* January 2010 up to January 2015. *Study design:* RCT or clinical controlled studies, cohort, case-control studies *Population:* human subjects <18 years old at baseline *Intervention or exposure and comparators:* studies with a measure of breakfast Primary outcomes Adiposity measures	Number of studies 12 studies (10 PCS, 1 intervention, 1 case-control) of which 1 PCS had participants aged 12 to 60 months at baseline. Number of participants The PCS of interest included 1366 participants Age of participants Participants were aged 2 years at baseline and followed up for 3 years Countries High income countries	Results of interest for the age group covered in this report The PCS of interest reported no association between skipping or eating breakfast and child weight status (see Annex 9, Table A9.33 for details).	Risk of bias or quality Review did not report whether or how studies were quality assessed. AMSTAR 2 overall confidence rating: critically low

Study	Methods	Included studies	Results	Comments
Brown et al (2016) 'Association of Picky Eating and Food Neophobia with Weight: A Systematic Review' Funding Supported, in part, by a grant from NICHD and NIH Mentored Patient-Orientated Research Career Development Award K23 HD061597 (Skelton) and from the Health Resources and Service Administration National Research Award (NRSA) grant T32 HP14001 (Brown, Vander Schaaf). Declaration of interests None to declare.	Research question To determine whether the presence of picky eating (PE) or food neophobia (FN) behaviours during childhood are associated with childhood weight status or with becoming underweight, overweight, or obese later in childhood and adolescence. Definition of 'picky eating' used: eating a limited variety of foods, but also covering fussy eating, food fussiness, and selective eating. Search criteria *Search dates*: from 1 January 1990 to 2 November 2015 *Study design:* No restrictions *Population:* children aged ≤18 years *Exposures:* PE or FN. Presence of PE determined through: - directly asking parents if their children were picky eaters - questionnaires: the 2 most common were the Child Eating Behaviour Questionnaire (CEBQ) and the Child Feeding Questionnaire (CFQ) - referral to a speciality feeding clinic for PE behaviours All studies that examined food neophobia (n=7) used the Child Food Neophobia Scale (CFNS) Primary outcomes Parental report of height and weight and measured height and weight	Number of studies 41 studies, of which 21 included children ≤6 years. Of the 21 studies, 4 were PCS (and the rest were CS). Number of participants Of the 4 PCS of interest, 2 studies included >100 participants, 2 included >400 participants and 1 included nearly 1500 participants. Age of participants Studies of interest included children aged 12 months to 4.5 years at baseline and followed up for 1 to 2 years. Countries High income countries	Results of interest for the age group covered in this report PE and weight status (4 PCS) - 2 of 4 PCS reported no association between PE and BMI or change in BMI; 1 reported a direct association between PE and change in BMI in girls only; 1 reported an association between PE and later odds of being underweight (see Annex 9, Table A9.33).	Risk of bias or quality Risk of bias and confounding assessed using the Agency for Healthcare Research and Quality's RTI Item Bank. Confounding factors Potential confounders (for example, demographics, family income, parental education) adjusted for in most studies, but other confounders (for example, parental weight status, feeding styles, community characteristics) often not adjusted for. Limitations (from the authors) Studies used inconsistent definitions of PE which limited the ability to combine the weight status data for meta-analysis. AMSTAR 2 overall confidence rating: moderate

Study	Methods	Included studies	Results	Comments
Caleza et al (2016) Childhood Obesity and Delayed Gratification Behavior: A Systematic Review of Experimental Studies' Funding Not reported. Declaration of interests None to declare.	Research question To evaluate the extent of the association between instant gratification behaviour and childhood obesity. Search criteria *Search dates*: up to October 2014. *Study design:* controlled clinical trials, experimental, or cohort controlled studies, with a sample size of ≥100. *Population:* Any human study or clinical research that included a sample of at least 100 children. *Intervention:* performance of a delayed gratification test involving a choice between a reward (food or non-food) granted immediately and a larger one later. *Comparison:* studies that compared the responses to the delayed gratification test in different populations of children. Primary outcomes - Definition of delayed gratification behaviour: a social ability that involves being able to resist the temptation to take a smaller but more immediate reward and to wait for a larger, more permanent reward later. - Children's self-regulatory ability to defer gratification measured by time to wait for the later larger reward (ranged from 2 minutes to next day).	Number of studies 9 studies (3 case control, 6 PCS), of which 2 PCS in children aged 12 to 60 months assessed the ability to delay gratification or self-regulate when offered a food reward Number of participants The 2 PCS of interest included 805 and 1061 participants Age of participants Children aged 3 to 4 years at baseline, followed up until adolescence (age 11 to 13 years) Countries High income countries	Results of interest for the age group covered in this report Both PCS reported an association between an inability to defer gratification and being overweight or obese in later childhood (see Annex 9, Table A9.33 for details).	Risk of bias or quality Assessed using the methodological index for non-randomised studies. Confounding factors Authors identified a number of confounding factors that might influence children's ability to delay gratification or regulate intake and impact on weight gain in childhood. These included: parenting style (permissive compared with authoritarian); parental weight status; negative life events; family environment (for example, difficult and chaotic home environment). The authors did not consider whether the studies had adjusted for these. AMSTAR 2 overall confidence rating: critically low

Study	Methods	Included studies	Results	Comments
	- Measure of obesity (BMI or skinfold thickness) measured at follow up			

Study	Methods	Included studies	Results	Comments
Hurley et al (2011) 'A systematic review of responsive feeding and child obesity in high-income countries' Funding National Institute of Child Health and Development Declarations of interest None to declare	Research question To summarise the evidence for associations between responsive feeding and child weight status in high-income countries; to describe responsive feeding measures; and to generate suggestions for future research Search criteria *Search dates:* 1990 to 2009 *Study design:* empirical research excluding case studies *Population:* 0 to 60 months *Intervention or exposure and comparators:* parental feeding, feeding patterns, feeding styles, eating patterns Primary outcomes Childhood overweight, weight status and growth patterns	Number of studies 31 studies, of which 3 (2 PCS, 1 repeated-measures) included participants aged 12 to 60 months. Of these 3 studies, the results from 2 that were reported in the SR have not been extracted in Annex 9 (Table A9.37) as these were from cross-sectional analyses. Number of participants The PCS of interest included 62 mother-child dyads Age of participants Participants were age 1 year at baseline and followed up after 1 year.	Results of interest for the age group covered in this report The PCS reported that pressure and restriction at age 1 year predicted lower child weight at 2 years (see Annex 9, Table A9.37 for details) Results for monitoring were not reported.	Risk of bias or quality Review did not report whether or how included studies were quality assessed. Limitations (from the review team) No studies identified on responsive feeding in children aged 12 to 60 months AMSTAR confidence rating: critically low

Study	Methods	Included studies	Results	Comments
Mikkelsen et al (2014) 'A systematic review of types of healthy eating interventions in preschools' Funding None specified Declarations of interest None to declare	Research question To review published literature on healthy eating interventions in day care facilities and analyse the effectiveness of different strategies in relation to their influence on children's food choice at an early age. Search criteria *Search dates:* Jan 1980 to 2014 *Study design:* intervention studies *Population:* healthy children aged 3 to 6 years (obese children were included) *Intervention and comparators:* interventions that focused on diet, nutrition, food, eating or meals in day care facilities Primary outcomes Food consumption patterns, knowledge and attitude towards foods and liking and willingness to try new food. Biological and anthropometric outcomes for example, BMI, serum cholesterol levels, skin-fold measurements, or prevalence of overweight and obesity	Number of studies 26 intervention studies of which 7 had a dietary or feeding component or measured child food preferences. Four of these were included in larger SRs with MAs (see Annex 7, Table A7.7 for mapping of primary studies) and were not extracted separately into Annex 9. Number of participants The 3 remaining studies (quasi-experimental) of interest included 38, 77 and 235 participants Age of participants Participants were aged 2 to 7 years Countries High income countries	Results of interest for the age group covered in this report Effect of feeding practices on food acceptance, preferences and intake (single interventions in preschool settings) - Peer modelling (1 study) - Portion sizes (2 studies) See Annex 9, Tables A9.1 and A9.36 for detailed results No studies were identified in the age group of interest that examined anthropometric outcomes.	Risk of bias or quality Study quality assessed using a rating scheme adapted from Cochrane and were rated according to the level of information available, study design, risk of bias, study population and study duration. Studies were rated from weak to very strong. Confounding Authors did not discuss the impact of confounding due to convenience sampling and non-randomisation in the studies of interest AMSTAR 2 overall confidence rating: low

Study	Methods	Included studies	Results	Comments
Mura Paroche et al (2017) 'How infants and young children learn about food: a systematic review' Funding Authors are employees of Nutricia Research Declarations of interest None declared	Research question To provide an overview of the developmental processes that are relevant to how children learn about food. To define the key gaps in the literature that need to be addressed if we are to increase our understanding of early food-related behaviour. Search criteria *Search dates:* February 2012 (initial search), February 2016 (additional search) *Study design:* human studies. Studies of food refusal, picky eating and other non-clinical 'problematic' feeding behaviours were included. Studies focusing on the development of a methodology were excluded, as were conference abstracts and position papers. *Population:* healthy children from weaning to 36 months old *Intervention or exposure and comparators:* studies relevant to a learning process in the food domain (those dealing with the pre-weaning milk-feeding period were excluded as were studies focussing on learning shown by parents, rather than children) Studies were categorised into 4 learning processes: (1) familiarisation; (2) observational learning; (3) associative learning; (4) categorisation. Primary outcomes	Number of studies 49 studies, of which 19 are within scope of this report and included participants aged 12 to 60 months. (As learning by categorisation is outside the scope of this report, data from categorisation studies were not extracted.) Of the 19 studies, 4 were included in SRs with MAs (see Annex 6, Table A6.4 for mapping of primary studies) and were not extracted separately into Annex 9. Number of participants The remaining 15 studies of interest, study sizes ranged from 16 to 151. More than half of the studies included <100 participants. Age of participants Of the 15 studies of interest, the age of participants ranged from 4 months to 5 years. Countries High income countries	Results of interest for the age group covered in this report Familiarisation with unfamiliar fruits or vegetables or textures: - Repeated taste exposure to vegetables (1 study) - Repeated taste exposure to a variety of textures (2 studies) - Repeated visual exposure (3 studies) See Annex A9, Table A9.34 for details Observational learning: - Peer modelling (2 studies) - Adult modelling (3 studies) - Maternal modelling of healthy eating on child eating behaviour and interest in food (1 study) See Annex A9, Table A9.36 for details Associative learning: - Early studies of flavour-flavour learning (FFL) and flavour-nutrient learning (FNL) suggested that children's liking and intake of target foods was influenced by their association with liked tastes or satiety signals. More recent studies that have compared the effectiveness of associative learning (for example, FFL and FNL) with repeated exposure have found no added benefit of conditioning. - Other forms of associative learning, such as pairing of a food with parental reward (direct association) or pressure to eat (inverse	Risk of bias or quality Study quality assessed using assessment criteria adapted from Jackson et al (2008). Quality criteria included whether there was a clear description or explanation of: (1) the design; (2) the scientific background and rationale; (3) the hypotheses and objectives; (4) the sample; (5) the data analysis; (6) the findings in relation to the hypotheses and objectives; (7) the provision of attrition or exclusion data, and appropriate handling of missing data; (8) the appropriateness of the experimental procedure; (9) consideration of methodological strengths; (10) consideration of the limitations of the study, and (11) the study's relevance for theories of learning about food. The quality criteria were used to exclude low-scoring outliers. Maximum quality assessment score: 11. AMSTAR 2 overall confidence rating: critically low

Study	Methods	Included studies	Results	Comments
	Learning about food		association) have been shown to impact on young children's willingness to consume the food. See Annex A9, Table A9.37 for details <u>Review's summary</u> The literature is consistent in demonstrating that conditioning techniques such as FFL or FNL provide no advantage over repeated exposure in shaping the food preferences of young children in the weaning and toddler periods. Repeated exposure is the preferred way to shape food preferences. Studies in older toddlers and school-aged children indicate that direct and inverse associations may be formed with foods.	

Study	Methods	Included studies	Results	Comments
Nekitsing et al (2018) 'Systematic review and meta-analysis of strategies to increase vegetable consumption in preschool children aged 2-5 years' Funding WRDTP ESRC Collaborative Award Declarations of interest None declared	Research question To investigate the effectiveness of interventions to increase vegetable intake in children aged between 2 and 5 years Search criteria *Search dates:* January 2006 to January 2016 *Study design:* intervention studies (RCTs, experiment or pre-post format) *Population*: children aged 2 to 5 years *Intervention:* articles included if vegetables were the only target food group (of the intervention) or were part of a health intervention (promoting healthy eating or physical activity) *Comparison:* no restrictions Primary outcomes Change in intake of vegetables (portions, grams; measured or reported) Statistical analyses - Random-effects model - Effect size quantified by Hedge's g (SMD) - Heterogeneity (I^2 statistic; values <0.25 considered low, <0.50 considered moderate, >0.75 considered high) - Subgroup analyses conducted based on study methodology, intervention factors (intervention strategies, type of vegetable, outcome measurements,	Number of studies 30 intervention studies (4 RCTs, 8 cluster-RCTs, 6 cross-over trials, 6 between-subjects, 3 within-subjects, and 3 pre-post format) Number of participants Total included in MA: 4017 Sample size range of individual studies: 12 to 1154 (or 902 post-intervention) Age of participants Mean age of children 3.8 years (based on 19 studies that reported the mean age) Countries Mostly high income countries (including 4 studies in the UK) Interventions - 9 strategies to promote vegetable intake (educational, taste exposure, pairing or stealth, provision of target foods or modification of portion size, use of rewards, modelling, choice offering, variety, visual presentation) - Type of vegetables included in the studies were classified as either: familiar or liked or unfamiliar or disliked - Intervention duration: 2 single sessions to 8 months.	Main results (as reported in the SR) See Annex 9, Table A9.34 for findings from the main MA and subgroup analyses. Effectiveness of taste exposure - Taste exposure had a greater impact on intake than education or other strategies which were also successful but to a smaller degree. - Main effect of taste exposure appeared to be most important as taste exposure alone had a greater effect than taste exposure combined with reward, reward alone or taste exposure combined with modelling. - Taste exposure to the vegetable on its own (plain form) produced a larger impact on intake than pairing with other flavours, dips or energy. - Findings on taste exposure from 4 studies which provided at least a full portion of the vegetable to the children and measured intake in grams indicated that on average children increased intake by 67g of the target vegetable (at least 1.5 portions of a child-sized portion of 40g) - Meta-regression analysis revealed that the number of taste exposures was directly associated with effect size; for a significant improvement in intake (a moderate effect of g = 0.5), children would require 8 to 10 exposures	Risk of bias or quality - Quality was assessed using the Effective Public Health Practice Project quality assessment toll for quantitative studies, which included 5 components: selection bias, study design, confounding, blinding, data collection methods, participant withdrawal and drop-outs - Funnel plot asymmetry and results of Egger's test suggested presence of publication bias Limitations (from the authors) - Significant heterogeneity observed across the 30 studies; additional subgroup analyses indicated that the moderators were possible sources (for example, type of vegetable used and intervention strategies) - Problem of multicollinearity made it difficult to determine whether taste exposure strategy or the use of an unfamiliar vegetable was more important in predicting intake - Limitation of using standardised effect size (Hedges g) is the clinical interpretation of the findings. - Limitations of the categorisation of vegetables into familiarity or liking categories include the potential overlaps between the vegetable categories (for example, a vegetable which is familiar can be disliked and unfamiliar foods are not necessarily disliked) - Literature search did not retrieve papers which specifically addressed fussy eaters even though the age range for the search included the peak period for fussy eating: future studies might investigate what specific strategies are effective in children who score high for neophobia or fussy eating

Study	Methods	Included studies	Results	Comments
	delivered by and the intervention recipient) - Meta-regression (random-effects) performed on a number of taste exposures used in the intervention - Publication bias (funnel plot and Egger's test)	Comparison no treatment (or baseline consumption), usual care or received treatment after the intervention phase		- Longer term studies needed to investigate if taste exposure strategies are sustainable over time, are feasible and cost-effective at a large scale AMSTAR 2 overall confidence rating low
Osei-Assibey et al (2012) 'The influence of the food environment on overweight and obesity in young children: A systematic review' Funding Good Places Better Health Initiative of the Scottish Government Declaration of interest None to declare	Research question To examine the evidence for environmental influences on dietary determinants of obesity, focusing on younger children (birth to 8 years). Search criteria *Search dates:* up to August 2011 *Study design:* population-based intervention studies or longitudinal studies *Population:* studies were included if the majority of the children studied were under 9 years *Intervention or exposure and comparators:* exposure to one of the environmental influences on dietary determinants of obesity (9 determinants identified, including desire for high palatable foods, large portions, high-energy snack foods and SSB) Primary outcomes - Child adiposity (BMI or body weight, skin-fold thickness, % body fat, per cent overweight or obesity - Dietary behaviours linked to obesity	Number of studies 35 studies, including 5 intervention studies (2 within-subject crossover studies, 2 non-randomised controlled trial) in children aged 12 to 60 months that involved a dietary or feeding component within the intervention. One study was included in the MAs by Hodder et al (2018) and Nekitsing et al (2018) and was not extracted separately into Annex 9. Number of participants Of the 4 remaining studies of interest, sample sizes ranged from 17 to 70 Age of participants Of the 4 studies of interest, ages ranged from 2 to 6 years old at baseline Countries High income countries	Results of interest covered in this report Portion sizes and child food or energy intake (3 studies) All 3 studies reported that large portion sizes increased child food or energy intake in the short term (2 to 3 months). Restrictive feeding practices and energy intake (1 study) The study did not find a relationship between restrictive feeding practices and child total energy intake See Annex 9, Tables A9.1 and A9.36 for details. No studies were identified for the age group of interest that examined child adiposity as an outcome.	Risk of bias or quality - Study quality was assessed using the Effective Public Health Practice Project quality assessment tool for quantitative studies. The tool was modified to take account of the design of the included studies - Results of the quality assessment of individual studies were not reported, although the authors did comment that several study samples in many non-RCTs and other experimental designs were convenience samples and not always representative of the target population or that only a small % of the samples agreed to participate - The review did not consider potential confounding from convenience sampling and non-randomised study designs AMSTAR 2 overall confidence rating: low

Study	Methods	Included studies	Results	Comments
Russell et al (2016) 'Effects of parent and child behaviours on overweight and obesity in infants and young children from disadvantaged backgrounds: systematic review with narrative synthesis' Funding Australian Government Department of Health and Ageing Declarations of interest None to declare	Research question To synthesise research on potential pathways through which disadvantaged infants and children aged up to 5 years and from OECD countries may experience greater weight gain, specifically focussing on the roles of parenting behaviours, children's eating, children's physical activity or sedentary behaviour as mechanisms for linking socioeconomic disadvantage and Indigenous status to greater weight gain in these groups. Search criteria *Search dates:* no restrictions *Study design:* studies involving human participants *Population*: children aged 0 to 5 years from low socioeconomic or Indigenous groups living in OECD countries without underlying medical conditions *Intervention:* interventions targeting parental nutrition knowledge, parenting styles or parental feeding practices in association with children's diets (studies focussing on weight loss were excluded) Primary outcomes child eating behaviours or weight	Number of studies 32 publications reporting on 31 studies (16 CS, 13 PCS, 1 RCT, 1 pre-post intervention), of which 3 PCS examined the relationship between parental feeding practices and eating behaviours or weight in children aged 12 to 60 months. Of the 3 PCS, results of 2 were not extracted into Annex 9 because these were from cross-sectional analyses. Number of participants The PCS of interest included 1797 participants. Age of participants Participants were aged 1 to 5 years at baseline (study duration NR). Countries High income countries	Results of interest for the age group covered in this report Parenting feeding practices and child weight The PCS reported no differences in feeding practices and child weight in Hispanic and non-Hispanic children after adjusting for parental and child ethnicity, and the sex of the child (see Annex 9, Table A9.37 for details).	Risk of bias or quality - Study quality assessed using the Mixed Methods Appraisal Tool (MMAT), comprising 2 screening questions (applied to all study designs) plus 4 questions (depending on study design) on sample selection, methods of measurement, completeness of outcome data, drop-out or follow-up rate. Quality ratings range from 0 to 4 (or 0 to 100%), where 4 (or 100%) indicates that all criteria were met. Limitations (from the authors) - Research in this area hindered by the availability of appropriate or adequate measurement tools for disadvantaged, ethnic minority populations - Clear definitions of concepts under study (for example, restriction) were often lacking and appeared to differ across studies. - As many of the parent and child behaviours associated with overweight co-occur, studies that isolate or control for confounding are needed to elucidate mechanisms of effect AMSTAR 2 overall confidence rating: moderate

Study	Methods	Included studies	Results	Comments
Ward et al (2015) 'Systematic review of the relationship between childcare educators' practices and preschoolers' physical activity and eating behaviour' Funding The first author funded by doctoral scholarships, including from the Canadian Institutes of Health Research Declaration of interest None to declare	Research question To identify if childcare educators' practices predict or are associated with preschoolers' physical activity and eating behaviours in childcare centres and to assess the effectiveness of interventions that control educators' practices or behaviours in order to improve preschoolers' physical activity and eating behaviours. Search criteria *Search dates:* until June 2015 *Study design:* all types of quantitative study designs (RCTs, quasi-randomised, non-randomised trials, cohorts, CC) *Population*: preschool aged children (between 2 - 5 years), receiving any type of formal, non-relative child care *Intervention:* included studies had to assess the unique contribution of childcare educators' practices or behaviours, on children's physical activity or eating behaviours Primary outcomes (of relevance to this report) - Child eating behaviours - Changes in diet or eating behaviour from baseline to follow-up (for experimental studies)	Number of studies 15 studies, of which 4 focused on nutrition and included participants aged 12 to 60 months (2 pre-post design, 2 quasi-experimental). Number of participants The 4 studies included 19 to 97 participants. Age of participants Not specified for individual studies. The authors defined 'preschooler' as any child aged 2 to 5 years old. Countries High income countries	Results of interest for the age group covered in this report Feeding practices for increasing children's acceptance of unfamiliar or familiar foods (including fruits and vegetables) - Adult modelling, silent compared with enthusiastic (2 studies) - Use of food or non-food rewards (2 studies) - Verbal encouragement (1 study) - Choice offering (1 study) See Annex 9, Table A9.36 for details of results.	Risk of bias or quality - Study quality assessed using the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies. Studies were assessed for selection bias, study design, confounding, blinding, data collection and withdrawals or dropouts, leading to a 'high', 'moderate' or 'low' rating. - Strength of evidence was assessed based on study design, methodology assessment and consistency of results. Limitations (from the authors) - Research into interventions to improve the eating behaviours of pre-schoolers lack consideration of demographic differences between groups - Most of the studies date from 2000 and earlier - Most of the studies of interest were small and measured children's eating behaviours by direct observation, which can be highly subjective and can lack precision at the individual level AMSTAR 2 overall confidence rating moderate

Excess weight and obesity

Table A5.6 Evidence table – excess weight and obesity

Study	Methods	Included studies	Results	Comments
Brisbois et al (2012) 'Early markers of adult obesity: a review' Funding Early Nutrition Committee, International Life Sciences Institute North America Declarations of interest None to declare	Research question To assess the literature to determine all potential prenatal, infant, childhood and sociodemographic markers which may have an impact on adult obesity. Search criteria *Search dates:* up to December 2009 *Study design:* quantitative studies *Population:* healthy children aged 0 to 5 years *Intervention or exposure and comparators:* - biomarkers as well as social determinants of health were considered (various measures of socioeconomic status, food security, gestational exposures, birth outcomes, developmental characteristics, behaviours) - variables must have been assessed at least once ≤5 years old Primary outcome Later obesity (assessed at least once in early to mid-adulthood (≥18 and ≤50 years of age).	Number of studies 135 studies that examined 42 predictor variables that were identified and categorised into the following: prenatal period, infancy, early childhood and sociodemographic factors. 15 PCS reported on childhood growth patterns (early rapid growth and early adiposity rebound) and childhood obesity. Number of participants Of the 15 PCS of interest, sample sizes ranged from 155 to 4306, with 9 studies including >100 to <500 participants; 3 studies including >500 to <1000 participants and 3 studies including >1000 participants Age of participants Of the studies of interest, children were aged 1 to 5 years at baseline in most of the studies; the age when measurements were taken in adulthood was not always reported Countries High income countries	Results of interest for the age group covered in this report Rapid early growth and risk of developing adult obesity (2 PCS) Both PCS reported an association between rapid early growth and risk of developing adult obesity (see Annex 9, Table A9.38 for details) Age at adiposity rebound and risk of developing adult obesity (4 PCS) All 4 PCS reported an association between early adiposity rebound (≤5 years of age) and higher risk of developing adult obesity (see Annex 9, Table A9.38 for details). Childhood obesity and adult overweight or obesity (11 PCS) 10 of 11 PCS reported a direct association between child BMI or overweight or obesity and (risk of) adult overweight or obesity (see Annex 9, Table A9.38 for details). Conclusions of review authors Strong, consistent findings were observed for childhood growth patterns and childhood obesity.	Risk of bias or quality Study quality not formally assessed by validated questionnaire although the review authors did consider: - statistical rigour, including type of statistics completed and if adjustments were made for confounding variables - type of study (prospective compared with retrospective) with the former considered more rigorous - measured compared with self-reported variables, with the former considered more objective and reliable Limitations (from the authors) - Many cohorts were initiated in the early half of the 20th century; as the obesity epidemic is a relatively recent phenomenon (last 3 decades), the environmental determinants of obesity may have changed substantially over the last 90 years. AMSTAR 2 overall confidence rating: critically low

Study	Methods	Included studies	Results	Comments
Llewellyn et al (2016) 'Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis' Funding National Institute for Health Research Health Technology Assessment Programme Declarations of interest None to declare	Research question To investigate the ability of childhood BMI to predict obesity-related morbidities in adulthood. Search criteria *Search dates:* up to June 2013 *Study design:* longitudinal cohort studies with at least 1000 participants at follow-up *Population:* no information on age or health condition *Intervention or exposure and comparators:* obesity in childhood Primary outcome Morbidities occurring in adulthood: cardiovascular diseases, hypertension, type II diabetes, metabolic syndrome or cancer. Statistical analyses - Outcomes pooled (if pre-specified morbidities were reported in ≥2 cohorts): adult-onset type II diabetes, coronary heart disease, stroke, hypertension, breast cancer. - Due to variation in reporting results, study estimates were converted into odds ratio (OD) per standard deviation (SD) of BMI to calculate pooled OR (random-effects model). The authors noted the following limitation with this approach – that it assumes that BMI follows a normal distribution and that	Number of studies 37 studies (reporting on 22 PCS). 7 PCS that included children aged ≤6 years at baseline were included in subgroup MAs for the following adult outcomes: - Diabetes (1 PCS) - Coronary heart disease (3 PCS) - Stroke (3 PCS) - Breast cancer (1 PCS) No studies in children aged ≤6 years were included in the subgroup analysis of childhood BMI and hypertension Sensitivity analyses performed only on 7 to 11 years and 12 to 18 years age groups. Countries High income countries (studies of interest)	Results of interest for the age group covered in this report See Annex 9, Table A9.39 for results of the MA	Risk of bias or quality Quality assessed using a modified version of the QUIPS checklist including assessment of selection bias, attrition bias, measurement bias, reporting bias and bias from confounding Confounding Review authors did not list key confounders but they did state that, where possible, results from models adjusted for confounding factors were used in the meta-analyses; models adjusted for adult obesity were not considered as the focus was to examine the association between childhood obesity and morbidity without knowledge of later adult obesity. Limitations (from the review authors) - Many identified cohorts commenced in the 1920s and 1950s but social conditions for children have changed considerably since that time; it is unclear whether the association between childhood BMI and adult morbidity from such cohorts accurately reflects the association in present-day children - Assumption of normality for BMI may be inaccurate; estimates of ORs should not be considered to be exact or definitive but instead indicate the general trend in results - Some cohorts may not have had sufficiently long follow-up to fully

Study	Methods	Included studies	Results	Comments
	the SD of BMI is the same in people with or without comorbidities.			capture adult morbidity-related events AMSTAR 2 overall confidence rating: critically low

Oral Health

Table A5.7 Evidence table – oral health

Study	Methods	Included studies	Results	Comments
Baghlaf et al (2018) 'Free sugars consumption around bedtime and dental caries in children: a systematic review' Funding No funding to declare Declaration of interest None to declare	Research questions (1) Does food or drink consumption at bedtime increase the risk of dental caries in children? (2) Does consuming foods containing free sugars at bedtime increase the risk of dental caries in children? (3) Does consuming drinks containing free sugars at bedtime increase the risk of dental caries in children? Search criteria *Search dates*: up to May 2017 *Study design*: RCTs, non-RCTs, prospective and retrospective cohort studies, case control studies, and cross-sectional studies *Population*: healthy children aged 3 to 16 years *Exposures*: any food and drink consumption around bedtime or before sleep – specifically, consuming food or drinks containing free sugars around bedtime. *Comparator*: no comparison group or a control group not exposed to food or drink around bedtime. Primary outcomes Dental caries or ECC assessed through clinical examination	Number of studies 18 studies (4 PCS, 1 CC, 15 CS), of which 1 PCS included participants aged 12 to 60 months. Number of participants The PCS of interest included 1782 participants Age of participants Participants were aged 3 to 6 years at baseline and followed up after 12 months Countries High income countries	Main result for the age group covered in this report The PCS of interest reported an association between the consumption of sweets at bedtime in children aged 3 to 6 years with greater odds of dental caries (see Annex 9, Table A9.47 for details). No studies were identified in children aged 12 to 60 months on consumption of drinks containing free sugars at bedtime and dental caries risk.	Risk of bias or quality - Study quality assessed using the AHRQ system and rated as 'good', 'fair' or 'poor' (domains assessed included: study population, comparability of subjects, outcome measurement, statistical analysis, funding). - The quality of the evidence evaluated using GRADE, and rated 'high', 'moderate', 'low' or 'very low'. - Publication bias (funnel plot) could not be assessed. AMSTAR 2 overall confidence rating: high

Study	Methods	Included studies	Results	Comments
Hermont et al (2015) 'Breastfeeding, bottle feeding practices and malocclusion in the primary dentition: a systematic review of cohort studies' Funding Research Foundation of the State of Minas Gerais (FAPEMIG), National Council of Technological and Scientific Development (CNPq), Brazilian Coordination of Higher Education, Brazilian Ministry of Education (CAPES), Pro-Reitoria de Pesquisa da UFMG (PRPq/UFMG). Declaration of interest None to declare	Research question Is bottle feeding associated with malocclusion in the primary dentition when compared to breastfeeding? Search criteria *Search dates:* no restrictions *Study design:* PCS *Population:* children in the primary dentition phase *Exposure:* bottle feeding *Comparator:* breastfeeding Primary outcome Malocclusion (MO)	Number of studies 10 PCS, of which 3 examined the association between breastfeeding or bottle feeding (>12 months) and odds of MO. To note that the results of 2 of the 3 studies of interest were also reported in Thomaz et al 2018 and have not been extracted here. Number of participants The PCS of interest included 120 participants at baseline and 80 at follow-up Age of participants Participants were aged 12 months at baseline and followed up at age 30 months Countries Upper middle income countries	Results of interest for the age group covered in this report The PCS of interest reported an association between bottle feeding at 12 months and 30 months and posterior crossbite at 12 months and 30 months (see Annex 9, Table A9.49)	Risk of bias or quality - Study quality assessed using Newcastle Ottawa Scale with the lowest possible grade=0 and the highest possible grade=10 - Publication bias was not quantitatively evaluated as there were not enough studies to be grouped in a funnel plot. Limitations (from the authors) - None of the studies included in the review performed a baseline oral examination to ensure that the participants were free of malocclusion. AMSTAR 2 overall confidence rating: moderate

Study	Methods	Included studies	Results	Comments
Hooley et al (2012a) 'Body mass index and dental caries in children and adolescents: a systematic review of literature published 2004 to 2011' Funding Not specified. Declaration of interest None to declare.	Research questions - What do studies reveal about the association between dental caries and BMI in children and adolescents? - What are the methodological limitations of the current approaches to investigating the development of both dental caries and obesity and what may be valuable directions for future research? Search criteria *Search dates:* January 2004 to June 2011 *Study design:* not specified *Population:* children and adolescents to age 18 years *Exposure:* some form of weight-to-height ratio to estimate body fat, for example, BMI, body fat index (DXA), Division of Nutrition, Thai Ministry of Public Health standards using weight-for-height in Thai children Primary outcome Measured caries rates	Number of studies 48 studies (8 PCS, 1 case control study, 38 CS, 1 retrospective case study) in 47 publications; 3 PCS included participants aged 12 to 60 months at baseline, of which 1 performed cross-sectional analyses which were not extracted here. Number of participants See results column Age of participants See results column Countries High income countries	Results of interest for the age group covered in this report Both PCS reported a direct association between child BMI and dental caries (see Annex 9, Table A9.50 for details) The review authors noted that the study did not provide sufficient detail about the sample and the regression model assumed a linear relationship. The sample therefore appeared to be positively skewed for dental caries and negatively skewed for BMI or body weight, with underweight participants significantly under-represented ($p<0.05$) compared with studies finding an inverse association or no association between BMI or body weight and dental caries.	Risk of bias or quality Studies evaluated on 3 criteria: representativeness of sample, control of potential confounding variables, quality of assessment of child weight-to-height and dental caries. AMSTAR 2 overall confidence rating: low

Study	Methods	Included studies	Results	Comments
Hooley et al (2012b) 'Parental influence and the development of dental caries in children aged 0-6 years: a systematic review of the literature' Funding Not specified Declaration of interest Not specified	Research questions - What parental variables have been studied within the context of dental caries development in young children aged 0 to 6y? - What do such studies reveal about the influence of parental variables on risk factors for dental caries in young children? - What are the relative strengths and limitations of current approaches to research studying the influence of parental variables in development of dental caries? - What recommendations can be made for future research? Search criteria *Search dates:* from 2006 to 2011 *Study design:* not specified *Population*: children aged 0-6 years old *Exposures*: parental factors were grouped into 6 categories, including parental feeding practices of children Primary outcome Early childhood caries (ECC), measure of dental caries prevalence or severity	Number of studies 55 studies (7 PCS, 1 case control study, 47 CS). Of the 6 exposure categories, only parent-child feeding practices were considered within scope of this report. 7 PCS in participants aged 12 to 60 months at baseline examined the association between parent-child feeding practices and dental caries development. Number of participants Of the 7 studies of interest, sample sizes ranged from 56 to 1576 Age of participants Most studies of interest included participants aged 18 months to 5 years. Population Majority conducted in high income countries and upper middle income countries	Results of interest for the age group covered in this report Parental-child feeding practices and ECC - Free sugars intake and ECC (1 PCS) - Foods and drinks containing free sugars and ECC (2 PCS) - Breastfeeding >12 months (1 PCS) - Use of infant feeding bottles for milk feeds (1 PCS) - Night time bottle feeding (2 PCS) - Use of infant feeding bottles to consume liquids containing free sugars (1 PCS) See Annex 9, Tables A9.40, A9.42 to A9.45, and A9.47 for detailed results	Risk of bias or quality Risk of bias assessed across 3 methodological attributes: dental caries diagnosis, statistical analysis (including whether potential confounding was controlled for) and sample characteristics (how representative samples were of the population under study); and ranked (A = highest possible rank; G = lowest possible rank). Limitations (from the review team) - Review did not provide quantitative data from the included studies making it difficult to assess the strength or magnitude of associations AMSTAR 2 overall confidence rating: critically low

Study	Methods	Included studies	Results	Comments
Moynihan and Kelly (2014) 'Effect on caries of restricting sugars intake: systematic review to inform WHO guidelines' <u>Funding</u> Newcastle University's Centre for Oral Health Research <u>Declaration of interest</u> None to declare.	<u>Research questions</u> - What is the effect on dental caries of reducing or increasing free sugars intake in children? - What is the effect on dental caries of restricting sugars intake to below 10% energy to reduce risk of dental caries in children? To note that the research questions were also applied to adults. <u>Search criteria</u> *Search dates*: 1950 to November 2011 *Study design*: RCTs, intervention studies, and observational studies; reviews were included if they contained a new analysis of existing data *Population*: healthy individuals (without acute illness, but those overweight or with hypertension or diabetes could be included) in developing, transitional, or industrialised countries; all age groups included *Exposures and comparators*: any intervention intended to alter sugars intake in one arm of the study compared with diet with a different sugars content in another study arm; observational studies were included if they reported absolute sugars or change in sugars intake; all timescales were included; sugars defined as any of total sugars, free sugars, added sugars, sucrose, non-milk extrinsic sugars, expressed as g or kg per day or per year or as % of energy <u>Primary outcomes</u> Caries prevalence, incidence or severity	<u>Number of studies</u> 55 studies (1 intervention, 8 PCS, 20 population studies, 26 CS) of which 4 PCS included participants aged 12 to 60 months. <u>Number of participants</u> Of the 4 PCS of interest, 1 included >100 participants, 1 included >250 participants, 2 included >500 participants <u>Age of participants</u> Of the 4 PCS of interest, children were aged 1 to 4 years at baseline with follow-up time ranging from 1 to 4 years. <u>Countries</u> High income countries and upper middle income countries	<u>Results of interest for the age group covered in this report</u> Effect of increasing free sugars' intake on caries (4 PCS) - 3 of 4 PCS reported that higher sugars intake was associated with higher dental caries. Effect of restricting free sugars' intake to <10% energy on caries (2 PCS) - Both PCS reported an association between sugars intake >10% energy and higher caries compared with sugars intake <10% energy See Annex 9, A9.40 for detailed results.	<u>Risk of bias or quality</u> - Quality of the evidence assessed using GRADE. Evidence quality classified as 'high', moderate, 'low' or 'very low'. - GRADE assessments based on cohort studies only. <u>Limitations</u> (from the review team) - Unclear which method was used to assess risk of bias in the included studies, particularly selection and attrition bias. <u>AMSTAR 2 overall confidence rating</u>: high

Study	Methods	Included studies	Results	Comments
Tham et al (2018) 'Breastfeeding and the risk of dental caries: a systematic review and meta-analysis' Funding World Health Organization Declaration of interest None to declare.	Research question To summarise the current evidence for the association between breastfeeding and dental caries, with reference to specific windows of early childhood caries risk. Search criteria *Search dates:* until 2 October 2014 *Study design:* observational and experimental studies published in full text *Population*: children and adolescents from both general and high-risk populations (for example, low socioeconomic communities) *Interventions or exposures:* breastfeeding compared with formula or other feeding Primary outcome Development of dental caries in deciduous or permanent teeth Meta-analysis - Random effects model used if heterogeneity I^2 >25%. - Heterogeneity (I^2) considered high if I^2=75%.	Number of studies 63 studies (14 PCS, 6 nested within RCTs of breastfeeding promotion interventions; 3 CC; 46 CS), of which 4 PCS examined the relationship between breastfeeding >12 months on caries risk in primary dentition and 1 PCS investigated the effect of breastfeeding >12 months on caries risk in primary and permanent dentition Number of participants Of the 4 PCS of interest, the sample sizes ranged from 163 to 922, with most studies between 300 to 500. 1 PCS did not report the number of children enrolled in the study but did report the number of pregnant women in the study (n=715). Age of participants Of the 4 PCS of interest, 38 months to 10 years at follow up. Countries High income countries and upper middle income countries	Results of interest for the age group covered in this report 2 of 2 PCS reported that BF for 12 months and longer was not associated with later ECC or S-ECC risk compared with BF for <6 months 3 of 3 PCS reported that BF for 18 months and longer was directly associated with ECC risk compared with not BF at 18 months. 2 of 2 PCS reported that BF for 24 months and longer was directly associated with ECC risk compared with not BF at 24 months See Annex 9, Table A9.42 for detailed results.	Risk of bias or quality - Study quality assessed using the Newcastle Ottawa Scale, with a maximum score = 10 (for PCS) and =7 (for CS). - Studies classified 'unsatisfactory' (scoring <4); 'satisfactory' (scoring 4 but lacking consideration of key confounders). Higher quality studies (scoring ≥5) were limited by how exposure was ascertained as many studies used self-report questionnaires. - Assessment of risk of bias guided by the GRADE assessment of evidence quality. Limitations (from the authors) A lack of studies on children aged >12 months that simultaneously assessed caries risk in breastfed, bottle-fed and children not bottle or breastfed, alongside specific breastfeeding practices, consuming sweet drinks and foods, and oral hygiene practices limiting the authors' ability to tease out the risks attributable to each. AMSTAR 2 overall confidence rating: low

Study	Methods	Included studies	Results	Comments
Thomaz et al (2018) 'Breastfeeding versus bottle feeding on malocclusion in children: a meta-analysis study' Funding National Counsel of Technological and Scientific Development (CNPq); the Foundation for Scientific Research and Development of Maranhão (FAPEMA) Declaration of interest None to declare.	Research question Are the type and duration of breastfeeding, compared with other forms of feeding, associated with malocclusion (MO) in primary teething in observational studies? Search criteria *Search dates*: up to December 2015 *Study design*: observational studies *Population*: children of both genders aged 0 to 7 years with primary teeth *Exposures*: breastfeeding and exclusive breastfeeding *Comparators*: non-breastfed children or those who were bottle fed Primary outcomes MO, such as nonspecific MO, anterior and posterior open bite, anterior and posterior crossbite, overbite, overjet, crowding and molar and canine relationships, or others. Meta-analysis - All types of MO were combined and analysed as one outcome. - Random-effects model - Subgroup analysis according to study design and MO type - Sensitivity analysis performed by excluding studies with a high risk of bias - Publication bias (funnel plots and the inclusion of unpublished studies).	Number of studies 42 studies (32 CS, 6 PCS and 4 nested PCS) of which 8 studies (3 PCS or nested PCS, 5 CS) investigated breastfeeding ≥12 months and MO. Only MA of estimates from PCS (n=3) was considered. Number of participants 419 participants in the 3 PCS that investigated breastfeeding ≥12 months. Age of participants Of the 3 studies of interest, participants were aged from 3 to 5 years old Countries Upper middle income countries and high income countries (studies of interest)	Results of interest for the age group covered in this report See Annex 9, Table A9.49 for details.	Risk of bias or quality - Risk of bias assessed using the Quality Assessment Tool (QAT) for Observational Cohort and Cross-Sectional studies, which contains 14 items (unspecified). - Funnel plots suggested publication bias favouring studies with significant results. AMSTAR 2 overall confidence rating: moderate