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Nutrition-specific interventions for preventing and controlling anaemia throughout the life cycle: an overview of systematic reviews (Protocol)

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[Overview of Reviews Protocol]

Nutrition-specific interventions for preventing and controlling anaemia throughout the life cycle: an overview of systematic reviews

Katharina da Silva Lopes[1], Yo Takemoto[2], Maria N Garcia-Casal[3], Erika Ota[1]

[1]Global Health Nursing, Graduate School of Nursing Sciences, St. Luke's International University, Tokyo, Japan. [2]Department of Obstetrics and Gynaecology, School of Medicine, Juntendo University, Tokyo, Japan. [3]Evidence and Programme Guidance, Department of Nutrition for Health and Development, World Health Organization, Geneva, Switzerland

Contact address: Erika Ota, Global Health Nursing, Graduate School of Nursing Sciences, St. Luke's International University, 10-1 Akashi-cho, Chuo-Ku, Tokyo, 104-0044, Japan. e-i@umin.ac.jp.

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ABSTRACT

This is a protocol for a Cochrane Review (Overview). The objectives are as follows:

To summarise the evidence from systematic reviews regarding the benefits or harms of nutrition interventions for preventing and controlling anaemia in anaemic or non-anaemic, apparently-healthy populations throughout the life cycle.

BACKGROUND

Description of the condition

Anaemia is defined as a decreased level of red blood cells, abnormal red blood cell morphology, or an inadequate amount of haemoglobin in red blood cells which, consequently, leads to an insufficient supply of oxygen in the body. It results from decreased red blood cell production (erythropoiesis), increased destruction, blood loss, or a combination of these factors. The underlying cause of anaemia (e.g. nutritional deficiencies, diseases, or genetic disorders) is frequently used to classify anaemia into nutritional and non-nutritional anaemia (WHO 2017). One of the most common causes of anaemia is iron deficiency, which is estimated to account for approximately 50% of all anaemia cases (Stevens 2013; Stoltzfus 2004). However, more recent estimates suggest that anaemia due to iron deficiency accounts for less than 50%, depending on the country-specific context (Petry 2016). Anaemia of chronic disease, another common type of anaemia, is multifactorial and its diagnosis generally requires the presence of chronic inflammation (i.e. infection, autoimmune disease, kidney disease, or cancer) (Weiss 2005). Numerous other nutritional and non-nutritional factors, in combination or isolation, have been associated with anaemia such as vitamin deficiencies (including folate, vitamin B_{12}, and vitamin A), inflammation, infectious diseases (i.e. malaria; soil-transmitted helminthiasis, especially hookworm infection; HIV; cancer; and tuberculosis), as well as genetic or acquired impairment of haemoglobin synthesis, and production and survival of red blood cells (Camaschella 2015; Lopez 2016). Anaemia may also be the result of physiological or pathophysiological acute or chronic blood losses. In menstruating women and adolescent girls, periods are the most common cause of iron deficiency anaemia (IDA), which, in some cases, may be excessive (i.e. menorrhagia, metrorrhagia) (WHO/CDC 2008). In men and post-menopausal women, bleeding in the gastrointestinal tract may be a common cause of anaemia (Lopez 2016). The health consequences of anaemia include fatigue during the early stages of the disease, coupled with a negative effect on productivity due to weakness, loss of energy, and dizziness. Anaemia also has an important impact on social and economic development due to loss of productivity (Bager 2014; Horton 2003). In addition, it is associated with adverse pregnancy and child outcomes (GBDPC 2016). Maternal anaemia may lead to greater blood loss during delivery, increased risk of postpartum haemorrhage, and maternal mortality (Brabin 2001a). Anaemic mothers are at greater risk of delivering preterm babies and of having a low-birthweight infant (Allen 2000). Anaemia also impacts negatively the cognitive and motor development of children, and severe anaemia increases the risk of child mortality (Brabin 2001b).

Anaemia is a significant public health problem, with prevalence highest in South Asia and Central and West Africa (Stevens 2013). Estimates from the World Health Organization (WHO) indicate that 800 million children and women were anaemic in 2011 (Stevens 2013; WHO 2015). Although anaemia can occur throughout the life cycle, young children and pregnant women are the most vulnerable, with estimated prevalences of 43% and 38%, respectively (WHO 2015). Between 1993 and 2013, the global prevalence of anaemia improved by only 0.2% to 0.3% points (Kassebaum 2014; Mason 2013). This slow progress, coupled with the overall burden of anaemia, has lead to anaemia's inclusion in the global nutrition targets to improve maternal, infant, and child nutrition agreed by the World Health Assembly in 2012 (WHO 2014a); the second of the six global goals aims for a 50% reduction of anaemia in women of reproductive age by 2015 (WHO 2014b). In addition, anaemia is indirectly included in the Sustainable Development Goals (SDGs); according to the second goal on ending hunger, target 2.2 aims to end all forms of malnutrition by 2030, by addressing, in particular, the nutritional needs of children under five years of age, adolescent girls, pregnant and lactating women, and older people (UN 2015).

Blood haemoglobin concentration is most commonly used as indicator of anaemia, since it is relatively easy and inexpensive to measure. Whilst it alone cannot determine the underlying cause of anaemia, in combination with other measurements, the haemoglobin concentration can provide important information about the severity of iron deficiency (WHO/CDC 2007). The blood haemoglobin concentrations currently used by the WHO to define anaemia are: less than 110 g/L for children under five years of age and pregnant women; less than 115 g/L for children aged 5 to 11 years; 120 g/L for children aged 12 to 14 years and non-pregnant women; and less than 130 g/L for men (WHO 2011). In this overview of reviews, we will use the anaemia cut-offs defined by the WHO to summarise the benefits or harms of nutrition-specific interventions for preventing and controlling anaemia throughout the life cycle.

Description of the interventions

The reasons for anaemia development are diverse but poor nutrition is one of its main causes (WHO 2017). Iron deficiency is a common nutritional deficiency worldwide and jointly responsible for the high and persistent prevalence of anaemia. However, various other micronutrients may be lacking in inadequate and imbalanced diets and contribute to micronutrient deficiencies and the emergence of anaemia (WHO 2015; WHO 2017). Micronutrient deficiencies, alone or in combination, manifest when requirements cannot be satisfied through adequate provision, intake, or absorption of nutrients. To counter this, several different approaches that prioritise dietary improvement have been implemented at the population level, or are directly targeted to vulnerable groups such as infants, young children, and pregnant women. Nutrition-specific interventions that address the immediate determinants of anaemia, such as poor diet, and nutrition-sensitive interventions that address the underlying causes of anaemia, such as diseases or infections, aim to prevent and control nutritional anaemia (Ruel 2013). This overview of reviews will focus on the former, and will include food-based strategies to control micronutrient malnutrition and increase the intake of micronutrients through supplementation, food fortification, and enhancement of food diversity and quality (WHO/FAO 2006; Zimmermann 2007).

Supplements are taken orally and are intended to supplement the diet with varies micronutrients, alone or in combination, at higher doses, to immediately improve nutritional deficiencies and anaemia (Stoltzfus 1998). Fortification refers to the addition of nutrients to food (e.g. in the form of powders) and beverages, and is another practical way to improve the diet of target populations (WHO/FAO 2006). These interventions show less immediate impact but are more sustainable and cost-effective over the long term (Baltussen 2004; WHO/FAO 2006). Nutrition education, counselling, and promotion aim to increase the intake of foods that are naturally high in certain micronutrients with high bioavailability (i.e. the degree to which the micronutrient is absorbed from the diet and available for the body's functions), and have a high content of factors to improve absorption coupled with a low content of inhibiting factors for micronutrient absorption (WHO 2017). Increasing food diversity is the most desirable and long-lasting intervention, but efforts to improve dietary quality and to encourage behavior change may take a long time (Girard 2012; WHO/FAO 2006).

This overview of reviews will focus on the prevention and control of anaemia at all stages of the life cycle, and plans to include the nutrition-specific interventions listed below.

- Supplementation

◦ Daily or intermittent oral iron, vitamins, or any other mineral (especially vitamin B_{12}, folate, vitamin A, or provitamin A, but also vitamin C, vitamin E, zinc, etc.) supplementation alone or in combination

- Fortification

◦ Fortification of foods with vitamins and minerals (e.g. iron, folate, vitamin B_{12}, zinc, vitamin A) alone or in combination

◦ Use of multiple micronutrient powders (sprinkles or point of use fortification)

◦ Provision of supplementary foods containing macronutrients (e.g. protein supplementation) alone or in combination with micronutrients (e.g. lipid-based nutrition supplements)

◦ Provision of fortified complementary foods

◦ Provisions of fortified staple foods or beverages (i.e. water) with micronutrients

◦ Provision of micronutrient, biofortified foods with increased contents of micronutrients (e.g. iron, zinc, vitamin A)

- Improving dietary diversity and quality

◦ Increasing food variety through nutrition education and provision of foods rich in minerals and vitamins such as fruits, vegetables, and iron-rich foods (i.e. read meat, proteins)

◦ Nutrition education and use of iron-pot cooking and fish-shaped iron ingots

◦ General nutrition education and counselling (e.g. increasing the intake of micronutrient absorption factors and decreasing inhibitors of micronutrient absorption)

How the intervention might work

Supplementation

Supplements in the form of capsules or drops are provided to target populations (WHO/FAO 2006). In this way, micronutrients can be given in the desired quantity and in combination with high bioavailability.

Iron supplementation is used widely, either to prevent iron deficiency and anaemia in populations at risk (e.g. pregnant women and young children), or to improve the haemoglobin status of people with existing anaemia. Four different iron preparations are used frequently for oral supplementation: ferrous sulphate, ferric sulphate, ferrous gluconate, and ferrous fumarate. The efficiency of iron supplementation greatly depends on the prevalence of iron deficiency and anaemia in the area, and interventions have been implemented in both low- and middle-income countries. Populations at high risk of anaemia may especially benefit from iron supplementation; for example, supplementation during pregnancy can reduce the risk of maternal anaemia and iron deficiency; however, benefits for infants, such as a reduced risk of being born premature or with a low birthweight, are less clear (Peña-Rosas 2015). Oral iron therapy is often limited due to low adherence and the development of side effects such as nausea and epigastric pain (Beutler 2003). Alternatively, other iron supplementation regimes, such as lower dosage or intermittent supplementation, can be used to reduce the occurrence of side effects (Cavalli-Sforza 2005). In areas with an anaemia prevalence of 40% or higher, the WHO recommends 10 to 12.5 mg of elemental iron for infants and young children aged 6 to 23 months, 30 mg for preschool-age children aged 24 to 59 months, and 30 to 60 mg for school-age children aged 60 months and older, menstruating adult women and adolescent girls, given daily for three consecutive months in a year to prevent iron deficiency and anaemia (WHO 2016a; WHO 2016b). In settings with a lower anaemia prevalence, intermittent regimes (one supplement per week) of 25 mg of elemental iron for preschool-age children aged 24 to 59 months, 45 mg for school-age children aged 60 months and older, and 60 mg for menstruating women and adolescent girls for three consecutive months followed by three months without supplementation and restart of the supplementation after this period, have been recommended to improve the haemoglobin concentration and reduce the risk of anaemia in this target population (WHO 2017). For pregnant women in areas with a lower anaemia prevalence (less than 20%), the recommended elemental iron supplementation is 120 mg (with folic acid) once a week throughout pregnancy to prevent the development of anaemia (WHO 2017). A comprehensive systematic review showed that there was no evidence of a difference in the prevalence of anaemia for women receiving intermittent oral iron supplementation during pregnancy compared with daily supplementation; additionally, intermittent supplementation was associated with fewer side effects (Peña-Rosas 2015).

In addition to iron, various other micronutrients are important for proper function of hematopoesis, and deficiencies may contribute to the development of anaemia. Primarily, folic acid, vitamin A, and vitamin B_{12} supplements, given alone or in combination with iron supplementation, are used to prevent and control for nutritional deficiencies in conjunction with anaemia. Folic acid plays a central role in erythropoiesis and pregnant women especially are at high risk of folic acid deficiency (Fishman 2000). The WHO recommends daily folic acid supplementation of 400 μg with 30 to 60 mg elemental iron, or 2800 μg folic acid with 120 mg iron once a week, for menstruating women as well as pregnant women to prevent maternal anaemia, puerperal sepsis, low birthweight, and preterm birth (WHO 2016c). Vitamin A acts on several stages of iron metabolism; it increases iron uptake, iron mobilization, and erythropoiesis (Fishman 2000). Supplementation during pregnancy is associated with reduced maternal anaemia for women living in areas with a vitamin A deficiency (McCauley 2015). Likewise, vitamin B_{12} plays a crucial role in erythropoiesis, and severe vitamin B_{12} deficiency can lead to the development of megaloblastic anaemia (Fishman 2000). Vitamin B_{12} is only produced by microorganisms, thus putting vegetarians, vegans, and populations in settings with low intake of animal products at increased risk of vitamin B_{12} deficiency. There is no consistent recommendation for the daily dosage of vitamin B_{12} supplementation, but commonly 2.4 μg/day is recommended for an adult; a pregnant women should add 0.2 μg/day of vitamin B_{12} to the estimated daily requirement (de Benoist 2008; Van Sande 2013). Other vitamins and minerals (e.g. vitamin C, vitamin E, zinc, or copper) are also required for normal enzyme and hematopoietic function and deficiencies in isolation or combination with other vitamins and minerals may contribute to the development of nutritional anaemia (Fishman 2000). Micronutrients interact in the body to maintain normal physiological functions and poor diets frequently lack several micronutrients at the same time, suggesting that micronutrient deficiencies often occur together. A cost-effective way of delivering micronutrients, especially for pregnant women, is through multiple micronutrient (MMN) supplementation. The international MMN preparation, UNIMMAP, is used frequently and contains one recommended daily allowance (RDA) of 15 vitamins and minerals (vitamin A, vitamin B_1, vitamin B_2, niacin, vitamin B_6, vitamin B_{12}, folic acid, vitamin C, vitamin D, vitamin E, copper, selenium, and iodine with 30 mg of iron and 15 mg of zinc) (UNICEF 1999). While MMN supplementation during pregnancy has been shown to improve birth outcomes, such as low birthweight and small-for-gestational weight, there is no clear evidence for a risk reduction of anaemia (da Silva Lopes 2017; Haider 2017).

Fortification

Fortification enriches food with nutrients in order to improve the nutritional status of populations at risk of micronutrient deficiencies (WHO/FAO 2006). Mass fortification approaches can reach a large proportion of the population by adding micronutrients, such as iron, folic acid, vitamin B_{12}, or vitamin A, to commonly consumed foods (e.g. cereals, salt, milk) (WHO 2017). In contrast, targeted fortification aims to improve the diet of a particular subpopulation that is unable to consume high quantities of staple foods (i.e. infants and young children), or who have higher nutritional requirements (i.e. pregnant women, infants, children, elderly), or both (WHO 2017). Targeted fortification can include the fortification of complementary foods (primarily with iron, zinc, and calcium) for infants during the transition from exclusive breastfeeding to solid foods (PAHO 2003). Nutrients can be added to food prior to consumption, in the form of micronutrient powders or sprinkles (point-of-use fortification), or consumed in the form of lipid-based supplements which contain micronutrients, energy, protein, and essential fatty acids (WHO 2017). Instead of adding nutrients directly to foods, biofortification (through breeding techniques and genetic modifications) has been used to increase the nutrient content (i.e. iron, zinc, provitamin A, amino acids, or protein) of crops (e.g. cereals, legumes, tubers) during plant growth (WHO/FAO 2006). Iron fortification can include the addition of iron as salt or chelates, or the addition of iron-rich components, such as meat, to food products (Prentice 2017). Iron fortification produces some technical difficulties as the addition of the most bioavailable forms is more expensive, causes unwanted flavour and colour changes, and may react with other food components (Hurrell 2002). Hence, less reactive and less expensive iron forms are chosen for fortification, but these forms are also less bioavailable (Hurrell 2002; Zimmermann 2007). Iron doses used for fortification are lower compared with supplementation and, accordingly, body iron levels increase much slower; however, fortification may be overall the safer intervention (Prentice 2017). Most commonly, wheat and maize flour, infant formula, and cereals are fortified with iron (WHO 2016d; WHO/FAO 2006). Other micronutrients, such as folic acid or B vitamins, are also commonly added to wheat flour. Vitamin A has been successfully added to milk or sugar to prevent vitamin A deficiency (Dary 2002).

Improving dietary diversity and quality

Insufficient dietary intake or poor bioavailability, especially of iron, vitamin A, vitamin B_{12}, and folate, are the major causes of nutritional anaemia (WHO 2017). Nutrition education and counselling (e.g. meal preparation, increased intake of micronutrient absorption factors and decreased intake of inhibitors), combined with the provision of foods rich in minerals and vitamins such as fruits, vegetables and iron-rich foods (i.e. read meat, proteins), aim to stimulate behavior change and to improve dietary diversity and quality (Allen 2008). These food-based approaches are potentially simple and sustainable methods for preventing and treating not only IDA but also micronutrient malnutrition, though implementation may be challenging due to limited availability, access, and safety of food (WHO 2017). When educating people in different areas of the world, health educators need to understand micronutrient nutrition and also regional and local variations in the diet; different cultural practices; different methods of food processing and meal preparation; and economic constraints (Sharifirad 2011; WHO 2017). Furthermore, these interventions need to take into account the special requirements of subpopulations and vulnerable groups (i.e. young children, pregnant women, elderly).

Examples of iron-rich foods include foods of animal (meat and organs from cattle, fish, fowl, etc.) and non-animal (spinach, legumes, and green leafy vegetables) origin. The availability of dietary iron can be influenced by various dietary factors and it is important to promote the consumption of foods that enhance the absorption and utilization of iron and reduce the intake of inhibitors. Ascorbic acid enhances iron absorption through its iron reducing and chelating effects (Teucher 2004). On the other hand, food components such as phytate (e.g. in cereals) and calcium can inhibit iron absorption (Lynch 2000). Additionally, milk proteins, egg proteins, and albumin negatively influence iron absorption (Hurrell 2010). Previous studies showed that nutrition education programmes can improve a study population's knowledge, attitude, and eating behaviour, as well as haemoglobin levels (Nandi 2016; Yusoff 2012; Sharifirad 2011). In some regions, fish-shaped iron ingots named "Happy Fish" or "Lucky Iron Fish" are commonly accepted for continuous use in soup or boiling drinking water (Adish 1999; Armstrong 2017). Cooking with iron ingots has been shown to release sufficient iron to provide 40% to 75% of the daily iron requirement for women of reproductive age. The duration of boiling iron fish coupled with the water's acidity increases iron release; any toxicity with daily use has not been reported (Armstrong 2017; Charles 2011).

The dietary requirements of vitamin A (retinol) and pro-vitamin A (carotenoids) can be attained by consumption of dark green leafy vegetables, orange/yellow fruits and vegetables, as well as animal products such as meat, liver, margarine, fish and fish oils, and dairy products. The fat-soluble vitamin needs to be consumed with lipids to improve its absorption and it is recommended that cooking time is reduced to preserve the activity of pro-vitamin A (WHO 2017).

Meat, fish, poultry, and dairy products are the best sources of vitamin B_{12}. Folate-rich foods include dark green leafy vegetables, fruits and fruit juices, dairy products, beans, nuts, and grains.

Why it is important to do this overview

Anaemia is a major public health problem worldwide. Anaemia prevalence fluctuates according to varies factors, including age, living area, sex, and socioeconomic status. Some types of anaemia are preventable and controllable with effective interventions. However, a limited number of studies have looked at the variety of nutrition-related interventions for controlling anaemia and iron deficiency throughout the life cycle. We will summarise different nutrition interventions at any stage of life in this Cochrane Review. It is important to assess the current evidence base to help clarify the best methods for preventing anaemia in order to reduce the socioeconomic burden of the condition.

OBJECTIVES

To summarise the evidence from systematic reviews regarding the benefits or harms of nutrition interventions for preventing and controlling anaemia in anaemic or non-anaemic, apparently-healthy populations throughout the life cycle.

METHODS

Criteria for considering reviews for inclusion

All published systematic reviews of randomised controlled trials (RCTs) of nutrition interventions for preventing and controlling anaemia.

We will include both Cochrane Reviews and non-Cochrane Reviews provided they have used a systematic approach, only included RCTs, and have assessed the methodological quality of the included trials. We will consider systematic reviews with and without meta-analysis but will exclude a meta-analysis without systematic review. We will list eligible systematic reviews in preparation (e.g. published protocols and titles) as 'awaiting classification' to be included in future updates of this overview of reviews.

Types of participants

Anaemic or non-anaemic, apparently-healthy populations (see directly below).

- Infants (aged six to 23 months)
- Preschool and school-age children (aged 2 to 10 years)
- Adolescent children (aged 11 to 18 years)
- Adult women
    - Non-pregnant women of reproductive age (aged 19 to 49 years)
    - Pregnant women of reproductive age (aged 15 to 49 years)
    - Older adult women (aged 50 to 65 years and above)
- Adult men (aged 19 to 65 years and above)

We will assign age groups according to the time when the interventions commenced. Where age groups overlap but data are presented separately, we will extract data according to age group. If this is not the case, we will use the mean age of the participants to assign the study into one of the pre-specified groups in such a way that most participants (e.g. 60%) fall within this group.

We will exclude infants younger than six months of age, since exclusive breastfeeding is recommended from birth until aged six months. In addition, we will exclude populations at risk of non-nutritional anaemia (i.e. participants with anaemia due to chronic disease, acquired bone marrow disorders, blood disorders, HIV infection), and studies conducted in populations comprising only individuals with undernutrition (i.e. wasting, stunting, underweight).

Types of interventions

All types of nutrition-related interventions (i.e. interventions that address the immediate determinants of nutrition) to prevent or correct anaemia, including the following.

- Supplementation
    - Daily or intermittent oral iron, vitamins, or any other mineral (especially vitamin B_{12}, folate, vitamin A, or provitamin A, but also vitamin C, vitamin E, zinc, etc.) supplementation alone or in combination
- Fortification

- Fortification of foods with vitamins and minerals (e.g. iron, folate, vitamin B_{12}, zinc, vitamin A) alone or in combination
  - Use of multiple micronutrient powders (sprinkles or point-of-use fortification)
  - Provision of supplementary foods containing macronutrients (e.g. protein supplementation) alone or in combination with micronutrients (e.g. lipid-based nutrition supplements)
  - Provision of fortified complementary foods
  - Provision of fortified staple foods or beverages (i.e. water) with micronutrients
  - Provision of micronutrient, biofortified foods with increased contents of micronutrients (e.g. iron, zinc, vitamin A, protein)

- Improving dietary diversity and quality
  - Increasing food variety through nutrition education and provision of foods rich in minerals and vitamins such as fruits, vegetables, and iron-rich foods (i.e. read meat, proteins)
  - Nutrition education and use of iron-pot cooking and fish-shaped iron ingots
  - General nutrition education and counselling (e.g. increasing the intake of micronutrient absorption factors and decreasing inhibitors of micronutrient absorption)

Types of comparisons

All types of comparisons, such as comparison of the intervention with placebo, another intervention (e.g. other minerals and vitamins), cointervention (provided the cointervention is the same in both the intervention and control groups), or no intervention (to correct anaemia levels directly or indirectly or control group defined by trial authors).

Types of outcomes

Primary outcomes

- Haemoglobin concentration (in g/L)
- Anaemia (defined per the WHO haemoglobin cut-off for age group (WHO 2011), and adjusted by altitude, smoking)
- IDA (defined by the presence of anaemia plus iron deficiency, and diagnosed with an indicator of iron status selected by trial authors)

Secondary outcomes

- Iron deficiency (defined by trial authors and measured using indicators of iron status such as ferritin or transferrin)
- Severe anaemia (defined per the WHO haemoglobin cut-off for age group (WHO 2011))
- Adverse effect (any adverse effects, including side effects, all gastrointestinal symptoms, diarrhoea, vomiting, constipation, defined by trial authors)

Search methods for identification of reviews

We will conduct electronic searches of the following sources.

- *Cochrane Database of Systematic Reviews* (CDSR; current issue) part of the Cochrane Library
- MEDLINE Ovid (1946 onwards)
- MEDLINE In-Progress and other Non-Indexed Citations Ovid (current issue)
- MEDLINE EPub Ahead of Print Ovid (current issue)
- Embase Ovid (1974 onwards)
- CINAHL EBSCOhost (Cumulative Index to Nursing and Allied Health Literature;1937 onwards)
- Database of Abstract of Reviews of Effects (DARE; 2015, Issue 4. Final Issue) part of the Cochrane Library
- Campbell Collaboration Online Library (campbellcollaboration.org/library.html)
- 3ie International Initiative for Impact Evaluation (www.3ieimpact.org)
- Epistemonikos (www.epistemonikos.org)
- POPLINE (www.popline.org)
- PROSPERO (www.crd.york.ac.uk/prospero)

We will search MEDLINE using the search strategy in Appendix 1, and will modify it accordingly to search the other databases. We will review the reference lists of the included reviews, as well as the references of relevant narrative reviews and guidelines, to find other relevant reviews. We will not apply any restrictions on language or publication date.

Data collection and analysis

The methods we intend to use for data collection and analysis, as described in successive sections, are based on Chapter 22 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of reviews

In order to identify all relevant published systematic reviews of RCTs assessing the effects of nutrition-specific interventions to prevent and control anaemia throughout the life cycle, two review authors (KL and YT) will independently screen titles and abstracts, and assess the full texts of all identified systematic reviews for eligibility. We will assess the reviews' objectives and methods, including outcomes and participants, for eligibility and include only those reviews that meet the criteria listed above (under 'Criteria for considering reviews for inclusion').

Where systematic reviews are similar in relation to research question, participants, and interventions, we will choose the most comprehensive review, provided there is an overlap between the underlying studies included in the individual reviews.
We will resolve any disagreements through discussion until we reach a consensus, or, if necessary, by consulting a third review author (EO).

Data extraction and management

We will generate a data extraction form and pilot test it. After verification, two review authors (KL and YT) will independently extract data from the included reviews on the following.

- Characteristics of included systematic reviews: date of search; numbers of participants and included trials; review objective(s); type of participants; setting (countries, anaemia and malaria prevalence); interventions; comparisons; relevant outcomes with definition and information for any adjustments; GRADE assessment of relevant outcomes
- Risk of bias assessment in included systematic reviews: method used; domains assessed; judgments
- Characteristics of interventions: population (mean age, anaemia status/prevalence, known micronutrient deficiencies); prevention or treatment; dosage or form of application (including compound, formulation); frequency; start and duration of intervention; adherence to intervention
- Results of included reviews: comparison; outcome; numbers of trials and participants; results (from meta-analysis or narrative description)

We will present the review details and results in tables according to age group and type of intervention. A third review author (EO) will verify the extracted data. We will resolve any discrepancies through discussion until we reach a consensus, or, if necessary, by consulting a third review author (EO).
Where any information from the reviews is unclear or missing, we will access the published papers of the individual trials. If we cannot obtain the details from the published papers, we will request the information from the individual review authors or authors of the original papers.

Assessment of methodological quality of included reviews

We will assess both the quality of evidence in the included reviews (by assessing the risk of bias of the included trials in each review and the GRADE quality ratings of the evidence, if provided), and the methodological quality of the systematic reviews (using AMSTAR: A MeaSurement Tool to Assess systematic Reviews).

Quality of the evidence in included reviews

Two review authors (KL and YT) will independently assess the quality of the evidence in the included reviews. We will summarise the methods used to assess random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. If provided in the included systematic reviews, we will also extract GRADE ratings for our primary and secondary outcomes, to assess the certainty of the evidence.

Quality of included reviews

Two review authors (KL and YT) will independently assess the methodological quality of the included reviews using AMSTAR (Shea 2007a; Shea 2007b; Shea 2009). AMSTAR assesses the degree to which review methods avoided bias by evaluating the methods against 11 distinct criteria (shown below).

- Was an a priori design provided?
- Was there duplicate study selection and data extraction?
- Was a comprehensive literature search performed?
- Was the status of publication (i.e. grey literature) used as an inclusion criterion?
- Was a list of studies (included and excluded) provided?
- Were the characteristics of the included studies provided?
- Was the scientific quality of the included studies assessed and documented?
- Was the scientific quality of the included studies used appropriately in formulating conclusions?
- Were the methods used to combine the findings of studies appropriate?
- Was the likelihood of publication bias assessed?
- Was the conflict of interest stated?

Each item on AMSTAR is rated as yes (clearly done), no (clearly not done), cannot answer, or not applicable. We will score each included review and assign a rating of 'high quality' to reviews with scores between 8 and 11; 'medium quality' to reviews with scores between 4 and 7; and 'low quality' to reviews with scores between 0 and 3. We will use this assessment to interpret the results of the reviews. We will resolve any discrepancies through discussion until we reach a consensus, or, if necessary, by consulting a third review author (EO).

Data synthesis

We will provide a narrative summary of the data from the individual reviews for our primary and secondary outcomes and present these summaries using tables. We will present data according to age group. Within each age category, we will summarise the results from the different systematic reviews according to the types of interventions (supplementation, fortification, improving dietary diversity and quality). We will describe the results separately for interventions versus placebo or no intervention, and interventions versus another intervention. We will investigate heterogeneity in relation to setting and population characteristics (e.g. prevalence of anaemia, malaria or other infectious diseases, baseline anaemia status, micronutrient deficiencies), features of the intervention (e.g. type, compound, dose, frequency, duration), and comparator (e.g. placebo, cointerventions, other interventions, no intervention). If the authors of the individual reviews have not adjusted the data on anaemia for altitude and smoking, we will present the data in the form provided and note this in the 'Results' and 'Discussion' sections of the review.

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* *Indicates the major publication for the study*

A P P E N D I C E S

Appendix 1. MEDLINE search strategy

1 exp Anemia/
2 (anaem$ or anem$ or non-anemic$ or non-anaemic$).tw,kf.
3 (iron$ adj3 (deficien$ or status)).tw,kf.
4 (haemoglobin or hemoglobin or Hb).tw,kf.
5 (ferric or ferrous or ferritin$ or Fe).tw,kf.
6 or/1-5
7 exp NUTRITION THERAPY/
8 Dietary Supplements/
9 Micronutrients/
10 exp foods, specialized/
11 diet/
12 food, fortified/
13 Biofortification/
14 iron/ or zinc/ or vitamin A/
15 (nutrition$ or diet$).ti.
16 (micronutrient$ or micro-nutrient$).tw,kf.

17 (multinutrient$ or multi-nutrient$ or multi$ nutrient$).tw,kf.
18 (multimicro-nutrient$ or multimicronutrient$).tw,kw.
19 (MNPs or MMPs or Sprinkles or Vita Shakti or Rahama or Anuka or Chispitas or BabyFer or Bebe Vanyan or Supplefer or Supplefem).tw,kf.
20 (multivitamin$ or multi-vitamin$).tw,kf.
21 (trace adj (element$ or mineral$ or nutrient$)).tw,kf.
22 iron, dietary/
23 Iron Chelating Agents/
24 ferric compounds/ or ferrous compounds/
25 (iron$ or zinc$ or "vitamin A" or retinol$).tw,kf.
26 (folic$ or folate$ or folvite$ or folacin$ or pteroylglutamic$).tw,kf.
27 exp Lipids/
28 (fatty acid$ or Docosahexaenoic acid$ or Eicosapentaenoic Acid$ or PUFA$ or lipid$ or omega 3$ or omega 6$).tw,kf.
29 (soy$ or wheat-soy$ or corn-soy$ or peanut or groundnut or whey or sesame or cashew or chickpea or oil$).tw,kf.
30 ((fortif$ or supplement$) adj3 (blend$ or diet$ or food$ or nutrition$)).tw,kf.
31 ((fortif$ or supplement$) adj3 (cereal$ or condiment$ or flour$ or legume$ or rice$ or salt$ or sauce$ or milk$ or formula)).tw,kf.
32 ("point of use" or point-of-use or "ready to use" or "ready -to- use" or RUSF$1 or RUTF$1) .tw,kf.
33 Weaning/
34 (complementary adj3 (feed$ or food$ or nutrition$)).tw,kf.
35 weaning.tw,kf.
36 (biofortif$ or bio-fortif$).tw,kf.
37 or/7-36
38 6 and 37
39 Anemia, Iron-Deficiency/dh, pc, th [Diet Therapy, Prevention & Control, Therapy]
40 38 or 39
41 Nutritional Sciences/
42 diet/
43 Diet Therapy/
44 Nutrition Therapy/
45 or/41-44
46 Health Education/
47 Health Knowledge, Attitudes, Practice/
48 health promotion/
49 Counseling/
50 or/46-49
51 45 and 50
52 ((nutrition$ or diet$ or food or feeding) adj3 (counsel$ or education$ or teach$ or class$)).tw,kf.
53 51 or 52
54 6 and 53
55 40 or 54
56 exp animals/ not humans/
57 55 not 56
58 meta-analysis.pt.
59 Meta-Analysis as Topic/
60 systematic$ review$.tw.
61 (metanalysis or metaanalysis or meta analysis).tw.
62 (metaregression or meta-regression or meta regression).tw.
63 (metasynthesis or meta-synthesis or meta synthesis).tw.
64 (realist review or realist synthesis or rapid review or pragmatic review or umbrella review).tw.
65 (Medline or Pubmed or Embase or Cinahl or Cochrane).ab.
66 ((literature or database$ or bibliographic) adj3 search$).ab.
67 ((inclusion or selection or predefined or predetermined) adj5 (studies or articles or reports)).ab.
68 or/58-67

69 57 and 68
70 limit 57 to systematic reviews
71 69 or 70

WHAT'S NEW

Date	Event	Description
20 August 2018	Amended	Correcting Maria García-Casal's DOI. See Declarations of interest.

CONTRIBUTIONS OF AUTHORS

Maria N García-Casal contributed to the design of the review. Katharina da Silva Lopes, Yo Takemoto, and Erika Ota drafted the protocol. All authors provided critical comments and valuable suggestions.

The contact author, Erika Ota, is the guarantor for the review.

DECLARATIONS OF INTEREST

Katharina da Silva Lopes: none known.

Yo Takemoto: none known.

Maria Nieves García-Casal (MNG-C) is a full-time member of staff at Evidence and Programme Guidance, Development of Nutrition for Health and Development, World Health Organization (WHO). MNG-C declares no other known conflicts of interest.

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