Micronutrient deficiencies, vitamin pills and nutritional supplements

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Abstract

In the 21st century, it is hard to reconcile the concepts of the western diet and overconsumption with the risk of micronutrient deficiencies. However, deficiencies can arise from poor dietary intake, alone or combined with physiological or metabolic injury. Micronutrients are essential to fulfil a broad range of biochemical and physiological functions, and are tightly regulated by homeostatic processes. Diagnosis of deficiency is complex and requires the use of separate investigations (dietary, functional, biochemical). While the role of micronutrients in the prevention or treatment of diseases (including cancer, type 2 diabetes) is of interest, a key driver for the vitamins and supplement market is their advertised potential to optimize health and performance in healthy individuals. The evidence so far indicates that multivitamins supplements offer no health protection, increase all-cause mortality, and risk of cancers in some subgroups. A nutritionally balanced diet is a safer way to achieve sufficiency.

Keywords

micronutrients, supplementation, recommendations, deficiency, antioxidant, evidence

M**icronutrients – intake, metabolism and storage**

There are 15 vitamins (11 water-soluble, and 4 lipid soluble) and 20 minerals (7 macroelements, 7 trace elements) essential for sustaining human life (Table 1). All vitamins and minerals can be obtained from a balanced diet that includes the main food groups. That diseases can arise from dietary deficiency has been well understood since the identification, in the 18th century, that supplementing the diet with citrus fruit could cure scurvy.

The physiological functions of micronutrients include acting as:

- co-enzymes in key metabolic reactions;
- antioxidants in the control of damage caused by reactive oxygen species;
- modulators of gene transcription;
- components of and co-factors for enzymes; and
- structural components of tissues (1).

The human body is highly adaptable with efficient homeostatic mechanisms, often under hormonal control, that balance the absorption, transport, storage, utilization and excretion of micronutrients. These mechanisms enable maintenance of appropriate circulating and stored reserves for use in tissue function. Such controls allow the body to function normally across a wide range of nutrient intakes, so that it can take some time before an overt deficiency disease materializes (Figure 1) (1).

For example the metabolic pool of calcium in the extracellular fluid (ECF) is very small compared with the large skeletal reserves, mobilization of which compensates for an inadequate intake of calcium. Conversely, there are no specific reserves for minerals such as zinc and the water-soluble vitamins, and the body is largely dependent on a regular supply in the diet. Interestingly, there is no physiological mechanism for iron excretion and iron balance is maintained through the regulation of its absorption from the diet. If iron is not required, it is stored in duodenal mucosal cells as ferritin and excreted in the faeces when mucosal cells are exfoliated.

The bioavailability of a nutrient can be defined as the proportion of that nutrient ingested from a particular food that can be absorbed and made available to the body for normal metabolic functions. This is the result of the interaction between the nutrient, other components of the diet (the food matrix) and the physiological status of the individual. For example, ascorbic acid (vitamin C) will increase non-haem iron absorption, as will the presence of haem iron in the duodenum and the iron deficient status of the individual. Conversely phytates, iron-binding phenolic compounds and replete iron stores will decrease absorption. Several vitamins and minerals, such as calcium, iron, zinc and a number of the B vitamins display such interactions.

Phytochemicals

Foods, especially plant foods, contain phytochemicals (including polyphenols, sterols), which are not recognized as nutrients but may have properties (e.g. antioxidant, anti-inflammatory or cholesterol-lowering) that are health-promoting. These properties have fuelled the expansion of the nutritional

supplement market, despite the European Food Safety Authority (EFSA) regulating the health claim market in Europe and requiring substantial evidence to justify claims (2).

The UK's Department of Health report on dietary reference values found no convincing evidence that it is necessary to include such compounds in a normal human diet and thus gave no further consideration to these or other unnecessary substances, including ornithine, orotic acid, lecithin, 'vitamin B_{15}' (pangamic acid), 'vitamin B_{17}' (laetrile), bioflavonoids (e.g. rutin, hesperidin, quercitin) or ubiquinones (coenzyme Q) (3).

Too much, too little – the U-shape relationship between micronutrients and health

A U-shape describes the dose-response relationship of micronutrients, with insufficient intake increasing the risk of deficiency, and excessive intake (acute and chronic exposure) increasing the risk of toxicity and associated diseases.

Countries worldwide, including the UK, have sought to publish dietary reference values (DRVs) (3). These recommendations are only an estimate at a population level, designed to be used as a yardstick for the assessment of dietary surveys and food statistics, for food labelling and to provide guidance on dietary composition.

In the UK, DRVs are set at a level needed to maintain a circulating concentration and a degree of enzyme saturation or tissue concentration of a given nutrient, in addition to ensuring that there are no clinical signs of a deficiency disease. This is a highly complex challenge, relying on many assumptions, including a nutrient's effects at different levels of intake, with individual requirements depending on age, gender and physiological state. DRVs are set on the assumption that individuals are in good health and not suffering from an existing deficiency. Where there is sufficient evidence, DRVs for micronutrients are set at a value believed the meet the needs of 97.5% of the population, known as the reference nutrient intake (RNI).

RNI values vary by age and gender. Additional recommendations are made for pregnancy, lactation and in old age for Vitamin D only (3).

(Figure 2) Different countries take a different approach to setting DRVs with their own terminology, creating confusion (e.g. RNI in UK, Recommended Daily allowance (RDA) in the USA and Population Reference Intake (PRI) in the EU) and resulting in inappropriate use of the recommendations.

There is insufficient evidence to set DRVs for some micronutrients, for example pantothenic acid, biotin, Vitamin E, Vitamin K, manganese, molybdenum, chromium and fluoride. In these cases the UK panel set 'safe intake' levels – a level or range of intake at which there is no risk of deficiency, but below a level that may produce undesirable effects.

Diagnosing deficiencies

Diagnosing deficiencies requires the integration of clinical/functional data (e.g. night blindness for vitamin A, lipid peroxidation for vitamin E, mean corpuscular volume for iron), dietary data (reported intakes, taking into consideration the risk of under/over-reporting) and biochemical data (e.g. plasma retinol for vitamin A, urinary iodine excretion). Comparison of intake with population thresholds (especially lower reference nutrient intake (LRNI)) is a first indicator of potential deficiencies, and may guide subsequent investigations. However, poor absorption or excretion can trigger deficiency in the presence of adequate intake (e. g. B_{12} deficiency). Infection and stress may also impact on nutritional status.

Biochemical analysis relies on collection of biological samples, most often plasma or serum, but also blood cells, urine, or hair. The impact of storage and handling on the stability of the analyte must be considered, and the analytical technique used should be specific, sensitive over the range of interest, robust, with normative data and quality controls available for interpretation and quality assurance (4, 5).

Are we at risk?

Overt deficiency diseases are relatively rare in industrialized countries, with the exception of iron deficiency and iron deficiency anaemia. Assessment of iodine status in UK schoolgirls indicated mild insufficiency at a population level, based on urinary iodine excretion (6).

The National Diet and Nutrition Survey (NDNS) reported that, on average, intakes of the majority of vitamins were adequate, as indicated by dietary intakes and biochemical indices of nutritional status, with some key exceptions (7) (Table 2).These results are at a population level and rely heavily on self-reporting of dietary intake, a notoriously imprecise methodology, and the health implications of such nutritional surveillance reports remain unclear.

Diet Quality

There are several components of diet quality, often confused. Terms such as 'healthy' have no definition, and are used only for marketing, often implying effect on body weight. The term 'nutritionally balanced' refers to diets, or meals, which have nutrient compositions which approximate to the dietary needs for optimal health. It is not useful to consider nutritional balance of individual foods or ingredients, which must be combined in different proportions to make up meals. For foods, the concept of 'nutrient density' can be valuable in nutritional science, referring to the density of nutrients *per unit energy* (per 1000kcal). This must be distinguished from density *per unit weight*, as used in food science. A high-quality diet has other cultural and economic features, so might be based on meals built on (wide, seasonal, locally sourced, unprocessed etc) selections of nutrient-rich foods, to match the reference intakes for all nutrients but without exceeding the reference energy intake.

Should we supplement?

The use of micronutrient pills and other nutritional supplements is currently suggested in three situations:

1. To correct deficiencies due to inadequate dietary intake (e.g. iron deficiency anaemia).
2. In disease states where requirements are enhanced (e.g. critically ill patients) or absorption compromised (e.g. Crohn's disease).
3. To promote health and performance, and protect against future chronic diseases in healthy individuals.

It is the last of these situations that is the most controversial and has the least clear evidence to support clinical decisions (8). Recommendations for supplementation in the healthy population are few, and includes, for example, folic acid before and during pregnancy and vitamin D in the young child. Despite the health claim market being tightly regulated by EFSA, and no recommendation being made, the use of vitamin pills and nutritional supplements generates almost US$50 billion globally (£751 million in 2013 in the UK) and is forecast to grow by 4% annually through to 2018 (9, 10).

Epidemiological studies, such as the EPIC prospective cohort study, have shown associations between vitamin supplementation and disease prevention (11). However, none of the randomized control trials reached the same positive conclusion, raising questions about the adequacy of dose setting and selected length of exposure in the trials with further concerns of systematic errors (12, 13). One exception is vitamin D, which has been associated with decreased mortality in elderly institutionalised women (14).

Meta-analyses of the available trials revealed that, beside there being no beneficial effect, some supplements could actually be harmful, with high doses of antioxidants such as β-carotene, vitamin A, vitamin E and multivitamins linked positively to all-cause mortality, although this association has sometime been disputed (15, 16). In two trials (the beta-carotene and retinol efficacy trial - CARET and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study - ATBC), high dose beta-carotene (20-30mg/day) caused increased incidence of lung cancer and mortality in male smokers (17, 18). Several hypotheses exist as to why beta-carotene supplementation was harmful in these trials, with no clear consensus so far. Potential mechanisms involve the interaction of high dose beta-carotene with cigarette smoke, and impaired retinoic acid mediated signal transduction, pro-oxidant action of beta-carotene in the oxygen-rich lung environment, and cytochrome P450 induction, all potentially contributing to tumour formation (19).

Besides being a potential waste of time and money for the healthy individual (20), supplementing with antioxidants to combat oxidative stress and ageing could also be an error if, as has been suggested, oxidative stress is a desirable feature (a low dose of the stimulus, oxidative stress, activating an adaptive response, ultimately to increase resistance to more severe stress) (21).

While supplementation to address a diagnosed deficiency, or through a specific stage of the lifecycle with increased needs is justified, the modern drive to use vitamin pills and supplements to prevent future disease and improve an otherwise healthy status is not supported by evidence, and can be

harmful for some.A nutritionally balanced diet provides all the essential vitamins and minerals and micronutrient levels in the body are tightly regulated by homeostatic processes.

Figure 1 | From depletion through deficiency to clinical manifestations (22)

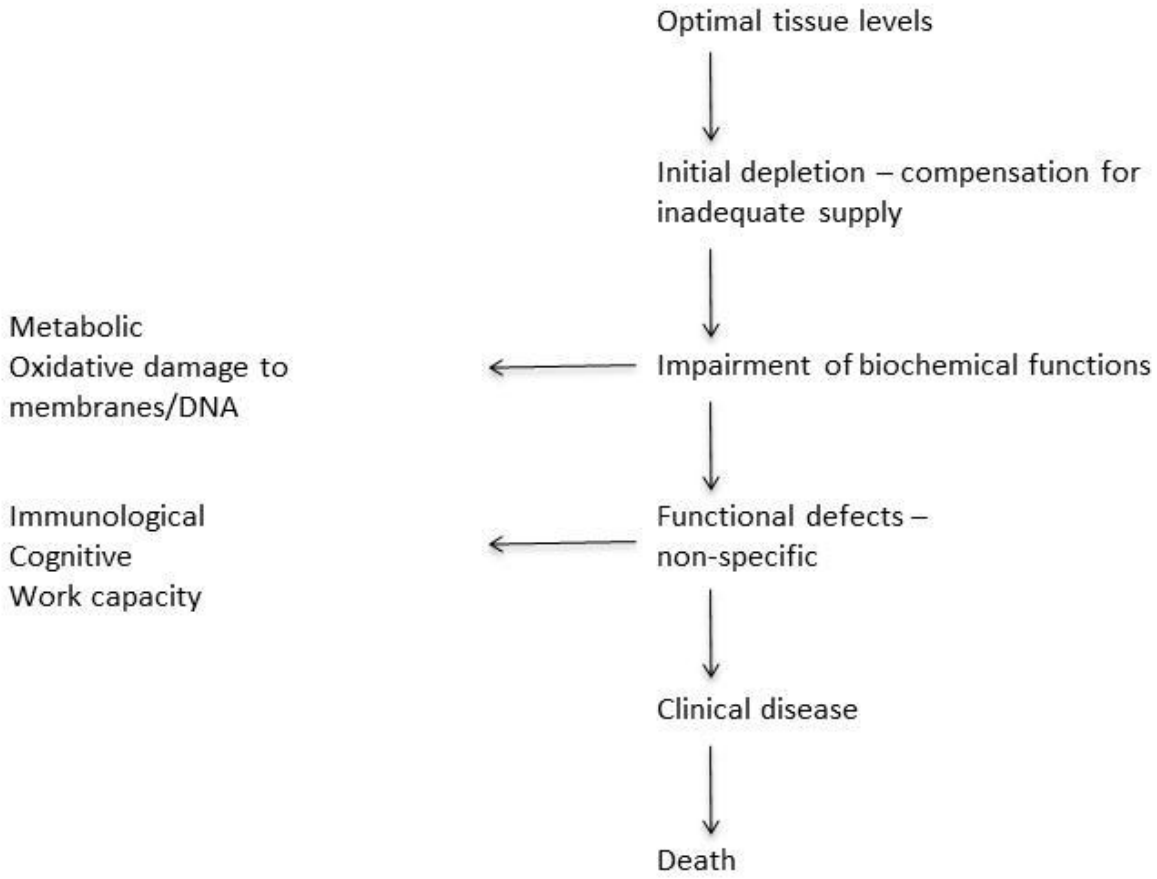
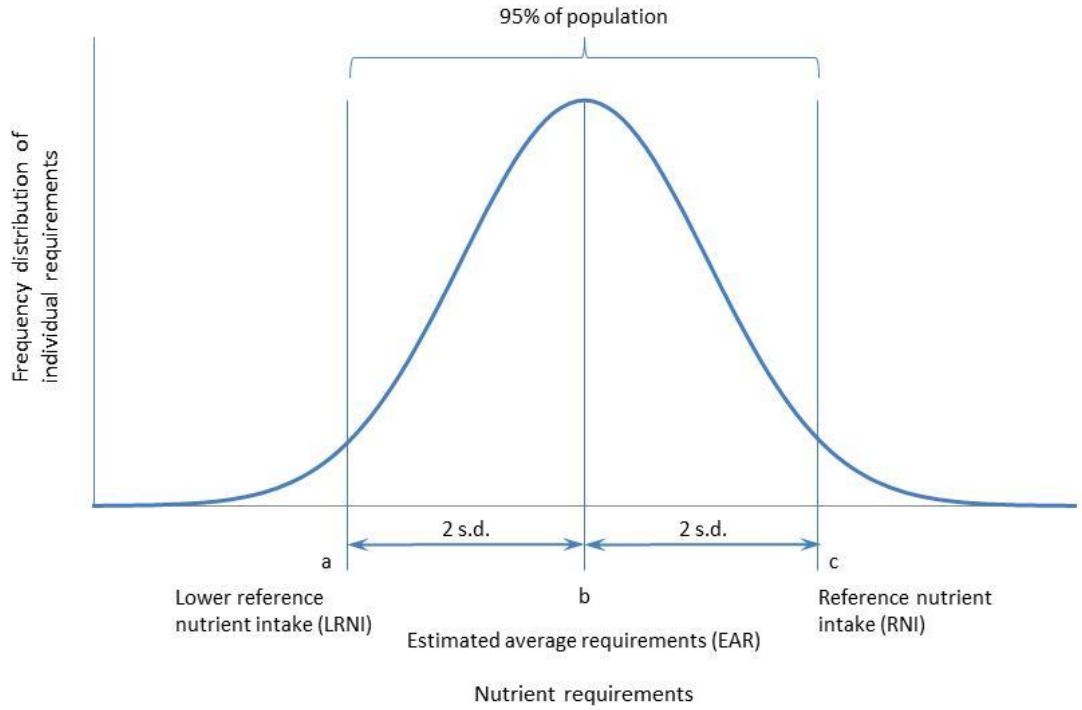


Figure 2| COMA dietary reference values and nutrient requirements (3)



(a) LRNI – level of nutrient intake that will meet the needs of approximately 2.5% of the population, habitual intake below LRNI will almost certainly be inadequate to meet individual needs.
Alternative terminology: EU - Lower Threshold Intake (LTI) USA - No equivalent

(b) EAR – the estimated average requirement (mean) for a group for a particular nutrient
Alternative terminology: EU - Average Requirement (AR) USA – Estimated Average Requirement (EAR)

(c) RNI – level of nutrient intake which is sufficient for 97.5% of the population, exceeds the requirement for most people and habitual intakes above RNI are almost certain to be adequate
Alternative terminology: EU – Population Reference Intake (PRI) USA – Recommended Daily Allowance (RDA)

Table 1 | Summary of micronutrient physiological functions and deficiency diseases

Vitamins	Physiological functions	Known deficiency diseases [a]	Possible benefits of high status(23, 24)
A - Retinol, beta-carotene	Visual pigments, gene expression, cell differentiation, antioxidant	Night blindness, xerophthalmia, keratinization of the skin	
D - Calciferol	Calcium homeostasis, cell maturation in small intestine, insulin secretion	Rickets (poor mineralization of bone), osteomalacia (demineralization of bone)	↓ Some cancers, diabetes, metabolic syndrome, multiple sclerosis
E - Tocopherols	Antioxidant, particularly in cell membranes	Rare - serious neurological dysfunction	↓ Atherosclerosis and ischemic heart disease
K – Phylloquinone, Menaquinones	Coenzyme for enzymes of blood clotting and bone matrix	Impaired blood clotting, haemorrhagic disease	
C - Ascorbic acid	Antioxidant, promotes iron absorption, collagen synthesis, production of noradrenaline, inhibits production of nitrosamines in stomach	Scurvy (impaired wound healing, loss of dental cement, subcutaneous haemorrhage)	↓ all-cause mortality
B1 - Thiamine	Co-enzyme in pyruvate and 2-keto-glutarate dehydrogenase and transketolase, Poorly defined role in nerve conduction	Beri beri (peripheral nerve damage), Wernicke–Korsakoff–syndrome (central nerve damage)	
B2 - Riboflavine	Co-enzyme in oxidation and reduction reactions, prosthetic group of flavoproteins	Lesions of corner of mouth, lips and tongue; seborrhoeic dermatitis	
Niacin - Nicotinic acid, Nicotinamide	Co-enzyme in oxidation and reduction reactions, functional part of NAD and NADP	Pellagra (photosensitive dermatitis, depressive psychosis)	
B6 - Pyridoxine, Pyridoxal, Pyridoxamine	Co-enzyme in transamination and decarboxylation of amino acids and glycogen phosphorylase, steroid hormone production	Disorders of amino acid metabolism, convulsions	
B9 - Folic acid	Co-enzyme in transfer of one carbon fragments	Megaloblastic anaemia, neural tube defects in babies	↓ Some cancers, especially colorectal cancer
B12 - Cobalamin	Co-enzyme in transfer of one carbon fragments and metabolism of folic acid	Pernicious anaemia (megaloblastic anaemia with degeneration of the spinal cord)	
Pantothenic acid	Functional part of coenzyme A and acyl carrier protein	Neuromotor disorders, mental depression, GI complaints and increased insulin sensitivity	
Biotin	Co-enzyme in carboxylation reactions in gluconeogenesis and fatty acid synthesis	Impaired fat and carbohydrate metabolism, dermatitis	

Minerals	Physiological functions	Known deficiency diseases[a]	Possible benefits of high status(23, 24)
Calcium	Skeletal growth and development, vascular and muscle contraction, nerve transmission, insulin release	Failure to attain peak bone mass, osteoporosis in later life	↓ Hypertension and colon cancer
Chloride	Hydrochloric acid in the stomach, chloride shift in erythrocyte plasma membrane, regulation of osmotic and electrolyte balances	Not diet related– only due to clinical conditions, eg: major trauma	
Chromium	Insulin action, carbohydrate, lipid and nucleic acid metabolism	Severe deficiency can cause insulin resistance	
Copper	Immune, nervous and cardiovascular systems, bone health, iron metabolism, haemoglobin synthesis, regulation of mitochondria, other gene expression.	Unlikely due to remarkable homeostatic mechanisms	↓ (speculation) cardiovascular disease and osteoporosis
Fluoride	Fluorapatite in teeth and bones	Increased risk of dental caries	
Iodine	Thyroid hormones growth and mental development, possibly antibiotic and anti-cancer	Goitre, hypothyroidism, cretinism (collectively termed iodine deficiency disorders)	↑Infection control and cancer prevention
Iron	Oxygen transport and storage, catalytic centre for a broad spectrum of metabolic functions cell respiration and energy production, immune system, myelination and nerve development in fetus	Iron deficiency and iron deficiency anaemia, impairment of the immune response, adverse effect on psychomotor and mental development in children	
Magnesium	Wide range of fundamental cellular reactions, >300 enzymatic steps in metabolism, skeletal development, gene regulation, nerve and muscle cell conduction	Only in diseased states or due to a rare genetic abnormality	↓ Cardiovascular disease, type II diabetes, hypertension, osteoporosis
Manganese	Catalytic co-factor for mitochondrial superoxide dismutase, arginase and pyruvate carboxylase	Rare - weight loss, dermatitis, growth retardation of hair and nails, decline of blood lipids	
Molybdenum	Co-factor for the iron- and flavin-containing enzymes that catalyse hydroxylation	Deficiency difficult to induce	
Phosphorus	Hydroxyapatite in calcified tissues, phospholipids in biological membranes, nucleotides and nucleic acid, maintenance of normal pH, storage and transfer of energy, activation of catalytic enzymes by phosphorylation	Hypophosphataemia resulting in cellular dysfunction – may include anorexia, anaemia, muscle weakness, bone pain, rickets and osteomalacia, general debility, increased infections, paraesthesia, ataxia, confusion	

Potassium	Major intracellular electrolyte – regulation of osmotic pressure and electrolyte balance, normal functioning of cardiovascular, respiratory, digestive, renal and endocrine systems, energy metabolism, cell growth and division	Low potassium intakes unlikely to lead to clinical potassium depletion and hypokalaemia except during starvation and anorexia nervosa	↓ Chronic heart failure and blood pressure
Selenium	Redox centre for the selenium-dependent glutathione peroxidases (antioxidant), thyroid hormone metabolism	Keshan's disease – a cardiomyopathy affecting children and women of child-bearing age	↓ Cancer incidence (particularly prostate), inflammatory conditions (e.g. rheumatoid arthritis, ulcerative colitis, pancreatitis, asthma)
Sodium	Major extracellular electrolyte – regulation of osmotic and electrolyte balances, nerve conduction, muscle contraction, energy-dependent cell transport systems, formation of mineral apatite of bone.	Not diet related – only due to clinical conditions, including major trauma	
Sulphur	Component of many proteins, energy metabolism as part of the electron transport chain		
Zinc	Catalytic, structural and regulatory roles, >100 metalloenzymes involved in energy metabolism, DNA & RNA synthesis, protein synthesis, expression of multiple genes, protection of mucosal cells, functioning of immune and reproductive systems	Growth retardation, sexual and skeletal immaturity, neuropsychiatric disturbances, dermatitis, alopecia, diarrhoea, susceptibility to infection and loss of appetite	↑Growth and development in children, ↓ risk of low birth weight and pre-term delivery

(a) Overt micronutrient deficiency diseases due to dietary insufficiency are rare, particularly in industrialised countries (more likely to be due to a clinical deficiency e.g. B12 deficiency caused by failure of intrinsic factor secretion).Worldwide the most common dietary deficiencies are vitamin A, iron and iodine (25)

Table 2| Main outcomes of the NDNS rolling survey 2008-2012 for micronutrients (7)

	Females (age group)				Males (age group)			
	4-10	11-18	19-64	65+	4-10	11-18	19-64	65+
Dietary intake (% of population with daily intakes <LRNI)[a]								
Vitamin A		14				11		
Riboflavin		20	11			9		
Folate		7						
Vitamin D[b]								
Iron		45	21					
Calcium		19						
Magnesium[c]		52	11			28	16	19
Potassium[c]		33	23	14		16	11	13
Zinc[c]	11	22				11		10
Selenium[c]		45	49	48		22	25	29
Iodine		22	10					
Biochemical data (% of population with plasma levels <threshold)								
Vitamin D[d]	16	24	22	24	12	20	24	17
Iron[e]	21	28	16		11			

[a] Population may be at risk of deficiency if a significance percentage has daily intakes below LRNI for a sustained period of time

[b] Insufficient evidence to set LRNI for Vitamin D

[c] Caution very limited data used to set DRVs

[d] Plasma concentrations of 25-hydroxyvitamin D <25nmol/L (threshold below which there is an increased risk of rickets and osteomalacia)

[e] Plasma concentrations of ferritin <15µg/L (threshold below which iron stores are considered to be depleted and the risk of iron-deficiency anaemia increased)

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