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). Although the role of micronutrients in preventing or treating diseases (including cancer and type 2 diabetes mellitus) 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 multivitamin supplements offer no health protection, and increase all-cause mortality, as well as risk of cancers in some subgroups. A nutritionally balanced diet is a safer way to achieve sufficiency.

Keywords Antioxidant; deficiency; evidence; micronutrients; MRCP; recommendations; supplementation; vitamin

Key points

- A nutritionally balanced diet provides all the essential vitamins and minerals
- Micronutrient levels in the body are tightly regulated by homeostatic processes
- Too much of certain vitamins or minerals can be as harmful as too little
- The dietary supplements market is in continuous expansion despite marketing regulations and lack of substantial evidence
- Although 'antioxidant' is an important concept in food science, there is no consistent evidence that food bioactives exert an antioxidant effect relevant to health *in vivo*
- Supplementation in healthy adults carries risks that are often ignored or dismissed

Micronutrients – intake, metabolism and storage

Thirteen essential vitamins (nine water-soluble, four lipid-soluble) and 16 minerals (including macro-elements and trace elements) are required for 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
- 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, usage and excretion of micronutrients. These mechanisms enable the 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 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 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 (sources including meat, shellfish and some legumes). Interestingly, there is no physiological mechanism for iron excretion, and iron balance is maintained by regulating 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.

A nutrient's bioavailability 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 individual's physiological status. For example, ascorbic acid (vitamin C) increases non-haem iron absorption, as does the presence of haem iron in the duodenum and an iron-deficient status. Conversely,

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Summary of micronutrient physiological functions and deficiency diseases

	Physiological functions	Known deficiency diseases
Vitamins		
A — retinol, β-carotene	Visual pigments, gene expression, cell differentiation, antioxidant	Night blindness, xerophthalmia, keratinization of the skin
D — calciferol	Calcium homeostasis, cell maturation in the small intestine, insulin secretion	Rickets (poor mineralization of bone), osteomalacia (demineralization of bone)
E — tocopherols	Antioxidant, particularly in cell membranes	Rare — serious neurological dysfunction
K — phylloquinone, menaquinones	Co-enzyme 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 (norepinephrine), inhibits production of nitrosamines in stomach	Scurvy (impaired wound healing, loss of dental cement, subcutaneous haemorrhage)
B_1 — thiamine	Co-enzyme in pyruvate and 2-keto-glutarate dehydrogenase and transketolase, poorly defined role in nerve conduction	Beriberi (peripheral nerve damage), Wernicke—Korsakoff syndrome (central nerve damage)
B_2 — riboflavin	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)
B_6 — pyridoxine, pyridoxal, pyridoxamine	Co-enzyme in transamination and decarboxylation of amino acids and glycogen phosphorylase, corticosteroid hormone production	Disorders of amino acid metabolism, convulsions
B_9 — folic acid	Co-enzyme in transfer of one-carbon fragments	Megaloblastic anaemia, neural tube defects in babies
B_{12} — 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 co-enzyme A and acyl carrier protein	Neuromotor disorders, mental depression, gastrointestinal complaints and increased insulin sensitivity
Biotin	Co-enzyme in carboxylation reactions in gluconeogenesis and fatty acid synthesis	Impaired fat and carbohydrate metabolism, dermatitis
Minerals		
Calcium	Skeletal growth and development, vascular and muscle contraction, nerve transmission, insulin release	Failure to attain peak bone mass, osteoporosis in later life
Chloride	Hydrochloric acid in the stomach, chloride shift in erythrocyte plasma membranes, regulation of osmotic and electrolyte balances	Not diet-related — only caused by clinical conditions (e.g. 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 because of remarkable homeostatic mechanisms
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)
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 the 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 caused by a rare genetic abnormality
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 — can 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 the cardiovascular, respiratory, digestive, renal and endocrine systems, energy metabolism, cell growth and division	Low potassium intake unlikely to lead to clinical potassium depletion and hypokalaemia except during starvation and anorexia nervosa
Selenium	Redox centre for the selenium-dependent glutathione peroxidases (antioxidant), thyroid hormone metabolism	Keshan's disease — a cardiomyopathy affecting children and women of childbearing age
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 — due only 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 and 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

NAD, nicotinamide adenine dinucleotide; NADP. nicotinamide adenine dinucleotide phosphate.

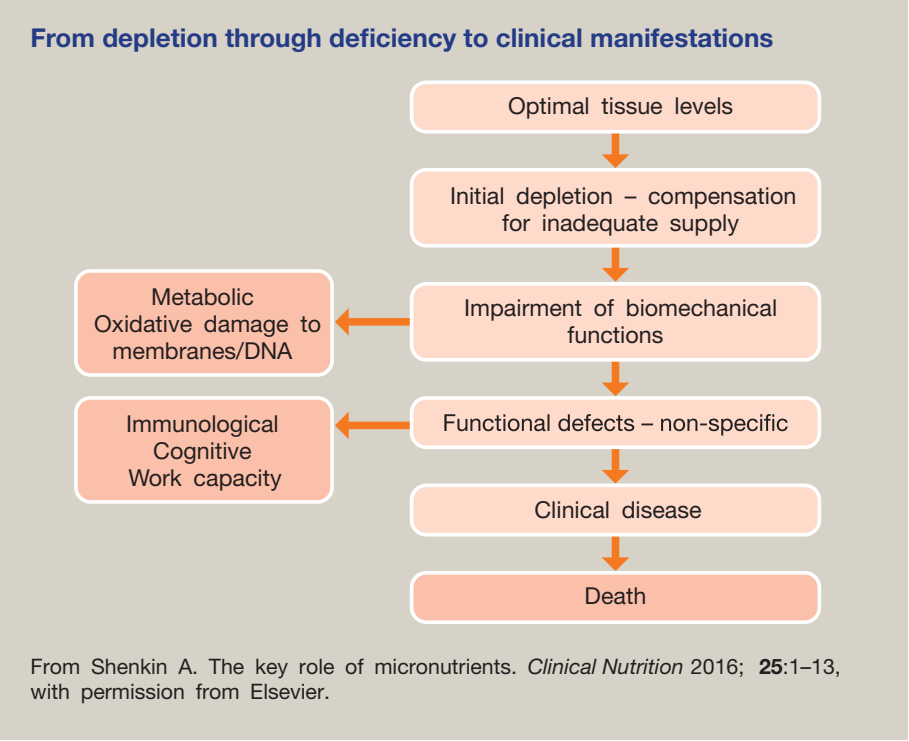
Table 1

phytates, iron-binding phenolic compounds and replete iron stores 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 and sterols), which are not recognized as nutrients but may have properties (e.g. anti-inflammatory, 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 the European Union and requiring substantial evidence to justify claims. The notion of food bioactives acting as 'antioxidant' is still relatively common, despite the fact that the antioxidant potential of these compounds is mostly relevant to food science. In fact, there is no consistent evidence that food bioactives exert an antioxidant activity *in vivo* that impacts on health.

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. It 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, quercetin) or ubiquinones (co-enzyme Q).[2] A large body of emerging research focuses on the impact of these compounds on health, with variability in effects linked to the food matrix, as well as to individual factors.



From Shenkin A. The key role of micronutrients. *Clinical Nutrition* 2016; **25**:1–13, with permission from Elsevier.

Figure 1

Too much, too little – the U-shaped 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).[2] 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 to 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 old age for vitamin D only.[2]

Different countries take a different approach to setting DRVs, using their own terminology, for example RNI in the UK, Recommended Daily Allowance in the USA and Population Reference Intake in the European Union (Figure 2). This tends to create confusion and results in inappropriate use of the recommendations.

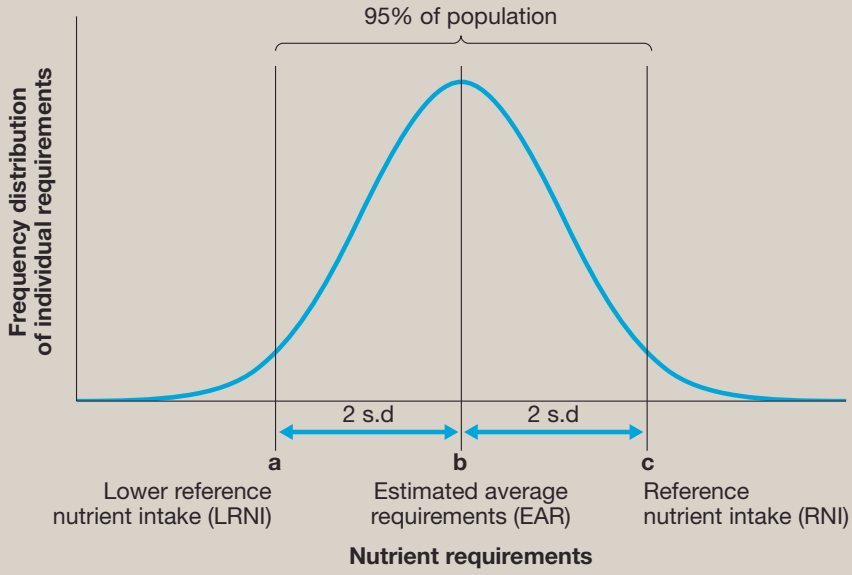
There is insufficient evidence to set DRVs for some micronutrients, for example pantothenic acid, biotin, vitamin E, vitamin K, manganese, molybdenum, chromium and fluoride. In these cases, the UK panel set 'Safe Intake' levels – levels or ranges of intake at which there is no risk of deficiency, but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

Diagnosing deficiencies

Diagnosis of deficiencies requires the integration of clinical/functional data (e.g. night blindness for vitamin A, lipid peroxidation for vitamin E, mean red cell 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). A comparison of intake with population thresholds (especially the Lower Reference Nutrient Intake (LRNI)) is a first indicator of potential deficiencies, and helps to guide subsequent investigations. However, poor absorption or excretion can trigger deficiency in the presence of adequate intake (e.g. B_{12} deficiency). Infection, inflammation and stress also affect the nutritional status.

Biochemical analysis relies on the 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. In addition, the analytical technique used should be specific, sensitive over the range of interest and robust, with normative data and quality controls available for interpretation and quality assurance.[3,4]

Committee on the Medical Aspects of Food Policy (COMA) dietary reference values and nutrient requirements[2]



(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)

SD, standard deviation.

Figure 2

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 the UK has indicated mild insufficiency at a population level, based on urinary iodine excretion, in schoolgirls and during pregnancy.

The National Diet and Nutrition Survey (NDNS) reported that, on average, intakes of most vitamins were adequate, as indicated by dietary intakes and biochemical indices of nutritional status, with some key exceptions (Table 2).[5] These results are at a population level and rely heavily on self-reporting of dietary intake, a notoriously imprecise methodology; the health implications of such nutritional surveillance reports therefore remain unclear. People following plant-based diets (up to 3.5 million people in 2017 in the UK) may need to focus on securing nutrients usually found in animal products, including vitamin B_{12}, calcium, iron, zinc and iodine, from alternative foods (sometimes fortified) or supplements.

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 an effect on body weight. The term 'nutritionally balanced' refers to diets, or meals, that have nutrient compositions approximating to the dietary needs for optimal health. It is not useful to consider the 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 1000 kcal). 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.

Main outcomes of the NDNS rolling survey 2014–2016 for micronutrients[5]

	Females (age group) (years)				Males (age group) (years)			
	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	11	24	10	7	13	19	16	6
Riboflavin	1	26	14	10	0	13	6	2
Folate	1	15	6	5	0	3	6	1
Vitamin D[b]								
Iron	3	54	27	10	0	12	2	1
Calcium	1	22	11	11	2	11	7	2
Magnesium[c]	3	50	11	18	0	27	14	13
Potassium[c]	0	38	23	27	0	18	11	9
Zinc[c]	14	27	8	7	9	18	7	7
Selenium[c]	1	45	47	66	1	26	25	36
Iodine	4	27	15	7	6	14	9	3
Biochemical data (% of population with plasma levels below threshold)								
Vitamin D[d]	7	28	11	10	7	15	3	14
Iron[e]	9/2	24/9	12/5	3/1	9/0	2/1	2/1	0/0

[a] Population may be at risk of deficiency if a significant percentage have daily intakes below the LRNI for a sustained period of time.
[b] Insufficient evidence to set an LRNI for vitamin D.
[c] Caution: very limited data used to set DRVs.
[d] Plasma concentrations of 25-hydroxyvitamin D <25 nmol/litre (the threshold below which there is an increased risk of rickets and osteomalacia).
[e] Plasma concentrations of ferritin <15 micrograms/litre (the threshold below which iron stores are considered to be depleted and risk of iron deficiency anaemia increased)/% below the threshold for both haemoglobin and plasma ferritin (haemoglobin: 1.5–4-year-old males <110 g/litre, 1.5–4-year-old females <110 g/litre, 5–11-year-old males <115 g/litre, 5–11-year-old females <115 g/litre, 12–14-year-old males <120 g/litre, 12–14-year-old females <120 g/litre, 15-year-old + males <130 g/litre, 15-year-old + females (non-pregnant) <120 g/litre).

Table 2

Should we supplement?

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

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

It is the last of these that is the most controversial and has the least clear evidence to support clinical decisions. Recommendations for supplementation in the healthy population are few, and include, for example, folic acid before and during pregnancy and vitamin D (UK adults and children over the age of 1 year should consider taking a supplement to achieve the daily recommended 10 μg of vitamin D). Despite the health claim market being tightly regulated by the EFSA, and no recommendation being made, the use of vitamin pills and nutritional supplements generates almost US$60 billion globally (the UK vitamins, minerals and supplements market alone was estimated at £421 million in 2016).

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

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

Besides being a potential waste of time and money for healthy individuals, supplementing with vitamins, minerals or other bioactive compounds (outside their usual food matrix) could interfere with normal physiological processes Although supplementation to address a diagnosed deficiency, or through a specific stage of the life cycle 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. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the question below. The answer can be found at the end of the issue or online here.

Question 1

A 50-year-old woman presented with fatigue and palpitations. She had had type 2 diabetes for 10 years. She was taking metformin. On clinical examination she looked pale but there were no other significant findings.

Investigations.

Haemoglobin 75 g/litre (115–165)
Mean corpuscular volume 116 fL (80–96)
Serum ferritin 400 micrograms/litre (15–300)
C-reactive protein 12 mg/litre (<10)

What is the most likely diagnosis?

A Anaemia due to B_{12} deficiency
B Anaemia due to folate deficiency
C Iron deficiency anaemia
D Anaemia of chronic disease/inflammation
E Haemolytic anaemia