Chapter 12
The B-Vitamins

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Abstract It is likely that future scenarios will see trends toward a reduced consumption of animal-based foods and increased consumption of fruit and vegetables. This chapter reviews the metabolic roles, essentiality, deficiency symptoms and food sources of each of the B-vitamins and identifies how trends towards improving environmental sustainability could impact on B-vitamin status.

Keywords Thiamine (vitamin B_1) · Riboflavin (vitamin B_2) · Niacin · Vitamin B_6 · Folate · Folic acid · Vitamin B_{12} · Choline · Biotin · Pantothenic acid · Metabolic roles · Essentiality · Deficiency symptoms · Food sources · Environmental sustainability

12.1 Introduction

There is increasing interest in nutrition and sustainability and how food policy and dietary guidelines might be modified to take into account issues related to environmental sustainability [36, 45, 47] as well as promoting healthy eating to prevent chronic disease. There is much debate on what constitutes a healthy diet, and many different dietary approaches could be taken to decrease environmental impact and improve sustainability. One approach is to concentrate on reducing consumption of animal-based foods and increasing the consumption of fruit and vegetables [77]. This approach is supported by the environmental impact literature indicating the sustainability of plant-based diets [81] and the need to increase the efficiency of land-based production of animal protein [103] and to control fish supplies [30]. Improvements in environmental sustainability by increased uptake of the Mediterranean Diet have also received attention [33]. Although there will be problems with meeting dietary guidelines attuned to a more sustainable agenda and there is continuing debate as to

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the optimum approach, it is likely that future scenarios will see trends towards a reduced consumption of animal-based foods and increased consumption of fruit and vegetables. This chapter will review the metabolic roles, essentiality, deficiency symptoms and food sources of each of the B vitamins, and will identify how trends towards improving environmental sustainability could impact on B-vitamin status.

12.2 Thiamin

Vitamin B_1, or thiamin, was the first of the B-vitamins to be identified, and occurs in the body as free thiamin or in one of its phosphorylated forms thiamin monophosphate (TMP), thiamin triphosphate (TTP) or thiamin pyrophosphate (TPP), also known as thiamin diphosphate (TDP) [7]. The majority—approximately 80% of ingested thiamin—occurs in humans as TDP, which plays a central role in the energy production from food. TDP acts as a co-enzyme for three key oxidative decarboxylation reactions: pyruvate dehydrogenase in carbohydrate metabolism, α-keto glutarate dehydrogenase in the citric acid cycle and α–keto-acid dehydrogenase in the metabolism of the branched-chain amino acids leucine, isoleucine and valine. Each dehydrogenase complex also requires a niacin and riboflavin containing co-enzyme. TDP is also required by the enzyme transketolase in the pentose phosphate pathway, an important alternative pathway of carbohydrate metabolism which generates the building blocks of nucleic acids, DNA and RNA and the niacin containing co-enzyme NADPH, essential for fatty acid synthesis [13]. Severe thiamin deficiency, rarely seen in developed countries, results in a disease called beriberi. Beriberi can occur as either dry or wet, with dry beriberi manifesting as neuropathy and muscle wasting while wet beriberi is characterized by congestive cardiac failure and edema in the lower limbs. It is of most concern in infancy due to the rapid growth and development that occurs in the early stages of the lifecycle. Wernicke-Korsakoff syndrome, which also occurs as a result of thiamin deficiency, is much more commonly reported in developed countries. The condition, which presents initially as a confused state, mainly affects chronic alcoholics but can also occur in those with gastrointestinal disorders, and if left untreated can lead to irreversible neurological damage and psychosis [53]. Supplemental thiamin is an effective treatment in most cases, if commenced in time.

Thiamin requirements are strongly associated with carbohydrate intake, given the role of the B-vitamin in carbohydrate metabolism. Requirements range from 1.0 to 1.4 mg/day and can usually be met by consuming a mixed or varied diet. Colonic microflora also produce thiamin, and while their contribution towards human thiamin requirements is currently not clear [51] it is undoubtedly an area of future interest in terms of sustainability. Rich sources of thiamin include wholegrain cereals, bread, lentils, beans, nuts, yeast and pork. Significant losses of thiamin occur during the milling process and during the processing of white rice, which has led to thiamin enrichment or fortification policies in many western countries [91];

such strategies are, however, not common in Asian countries. Heating foods can also reduce their thiamin content to some extent, and an enzyme known as thiaminase, present in raw fish, shellfish, tea and coffee, decreases thiamin absorption. Inadequate intakes of the vitamin have been observed in institutionalized older adults [102], in those with an alcohol dependency, and in countries where dietary sources of carbohydrate are high and thiamin intakes are low e.g. Southeast Asian countries such as Cambodia, where reported intakes are as low as 0.58 mg/day [100]. In terms of sustaining thiamin intake, fortification offers an effective model, However, strategies will need to be tailored to different populations on the basis of the relevant staple foods consumed [91].

12.3 Riboflavin

Riboflavin, also known as vitamin B_2, is a water-soluble vitamin and is the precursor of the coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), collectively known as flavin coenzymes. FAD and FMN participate in intermediary metabolism catalyzing numerous oxidation-reduction reactions involved in the metabolism of protein, fat and carbohydrates [55]. Flavin coenzymes are also required for the metabolism of iron and a number of B-vitamins—namely B_6, folate and niacin. FMN acts as a cofactor for the enzyme pyridoxine phosphate oxidase in the conversion of pyridoxine phosphate to its coenzyme form pyridoxal-5 phosphate (PLP) in vitamin B_6 metabolism. FAD meanwhile acts as a cofactor for the enzyme methylenetetrahydrofolate reductase (MTHFR) in the production of 5-methyltetrahydrofolate, essential for the remethylation of homocysteine to methionine [52]. Niacin synthesis is also reliant on the FAD-dependent enzyme kynurenine mono-oxygenase, which is required for the synthesis of the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) from tryptophan. Riboflavin deficiency decreases the conversion of tryptophan to NAD and NADP, resulting in a deficiency of niacin. In relation to iron metabolism, evidence from animal studies suggests that riboflavin deficiency can impair iron absorption and utilization for the synthesis of hemoglobin [74].

Clinical riboflavin deficiency (typically presenting as angular stomatitis, cheilosis and glossitis) is common in developing populations [4, 11] but rarely reported in Western societies, as intakes in the West are generally higher than dietary recommendations. What is less well recognized, however, is the emerging evidence indicating that sub-optimal riboflavin status may be much more wide spread in both developed and developing counties than previously considered [52]. The majority of population-based studies report dietary intake data, with only a limited number reporting biomarker riboflavin status. It appears, however, that despite apparently adequate riboflavin intakes, suboptimal status—as determined by the functional marker erythrocyte glutathione reductase activation coefficient

(EGRac)—may be quite common in many populations. Younger women, including pregnant and lactating women, and those who do not consume meat or dairy, appear to be most vulnerable. The significance of these findings is not clear; however, it is possible that marginal riboflavin status in the absence of clinical deficiency may have adverse functional effects and long-term consequences for health. Sub-optimal riboflavin status has been associated with preeclampsia in pregnant women [96]. More recently, a polymorphism in the riboflavin-dependent enzyme MTHFR, prevalent in 10% of adults worldwide but occurring in up to 30% of some populations, has been associated with hypertension [104, 105]. Furthermore, intervention with riboflavin has been shown to significantly decrease blood pressure in these genetically at-risk adults [41] and thus maintaining an adequate riboflavin status in these individuals could potentially delay the onset of hypertension [60].

Worldwide dietary recommendations for riboflavin range from 1.1 to 1.6 mg/day, with clinical deficiency signs appearing at intakes of between 0.5 and 0.6 mg/day [26]. The majority of riboflavin in food occurs in the form of FAD, with lesser amounts as FMN and free riboflavin. It is estimated that about 95% of riboflavin in the form of FAD or FMN is bioavailable, with absorption limited to approximately 30 mg of riboflavin at any one time [54]. The main dietary sources of riboflavin are milk and dairy products, while meat and fortified foods such as breakfast cereals also contribute significantly [29]. Yeast extracts are also a good source of riboflavin but are not consumed in large enough quantities to make a significant contribution to intake. Riboflavin intakes are thus likely to be low in populations consuming diets low in dairy and meat and could be limited in those consuming a vegetarian diet. In terms of maintaining a sustainable source of riboflavin, food fortification is likely to offer the most promising solution, although consideration would need to be given to the level of fortification introduced [1]. Riboflavin enrichment policies are currently in place in the US and Canada, to replace the riboflavin lost during milling in those countries; however, despite this practice, suboptimal status has been reported in certain subgroups [99].

12.4 Niacin

Niacin is a generic term for nicotinic acid and nicotinamide, which are substrates for the synthesis of the coenzymes nicotinamide adenine dinucleotide (NAD) and its phosphorylated derivative nicotinamide adenine dinucleotide phosphate (NADP). Both NAD and NADP are involved in oxidation and reduction reactions, which explains the crucial importance of niacin for energy metabolism. In addition, NAD also has non-redox functions and it is a key factor for various ADP-ribose transfer reactions which maintain genomic stability, DNA repair, gene expression, apoptosis, cellular signaling and insulin sensitivity [8, 46]. Deficiency of niacin results in pellagra, the clinical features of which include photosensitive dermatitis with skin lesions, inflammation of gastrointestinal mucosa with diarrhea, depression and dementia. Diarrhea further worsens niacin status and worsens the condition by

affecting also the absorption and status of other nutrients. Untreated pellagra can lead to death from multi-organ failure [95]. In the past, when the cause of pellagra was still unknown, the spread of the disease in Europe and the US led to epidemics, especially among poor communities with limited food availability where maize or millet were the dietary staples. In order to combat the widespread niacin deficiency, mandatory niacin flour fortification programs have been introduced in many countries of the world since the 1940s. Recent epidemiological surveys from developed countries have shown that the average intake of niacin is much above the dietary requirements [6, 69, 85], which explains the fact that pellagra is virtually unknown there and is only occasionally found in malnourished alcoholic patients. However, outbreaks of pellagra still occur nowadays in people with restricted normal movements and activities, e.g. in refugee camps or jails, where food intake may be limited [61].

Meat, poultry and fish have high content of niacin. In addition, animal foods are also important as they are rich in the amino acid tryptophan, which can be used for synthesis of niacin in the body. However, some plant foods such as nuts, legumes and cereals are also a very good source of preformed niacin as well as tryptophan. Significant contributors to dietary intake of niacin are fortified flour and breakfast cereals; however, niacin food fortification is not in place in some countries. The bioavailability of niacin from foods is generally high but in some cereals, notably maize, niacin is in esterified forms (niacytin) which are unavailable for absorption after conventional cooking [16]. However, the bioavailability of niacin from its bound forms can be considerably improved by pre-treatment of the food with alkaline solutions (lime water) before cooking. Analysis of the composition of so called 'pellagragenic' diets (containing mainly cereals) by applying an alkaline pre-treatment has found that their niacin content was well in excess of the dietary requirements for intake [15]. This finding suggests that environmentally sustained diets based on foods predominantly from plant origin have the potential to provide sufficient amounts of niacin for maintaining an adequate status.

12.5 Vitamin B_6

The term vitamin B_6 refers to a group of several water-soluble compounds with the biological activity of pyridoxine which are converted to each other in the body. The metabolically active vitamin B_6 derivatives, pyridoxal phosphate and pyridoxamine phosphate, act as cofactors for more than 100 enzymes involved predominantly in the metabolism of amino acids but also in one-carbon metabolism, glycogenolysis and gluconeogenesis, regulation of the function of the nervous system through synthesis of neurotransmitters, immune function, formation of niacin from tryptophan, hemoglobin synthesis, and modulation of steroid hormone activity. Severe deficiency of vitamin B_6 is uncommon. In the early 1950s, seizures were observed in infants who consumed low vitamin B_6-containing milk formula as a result of an error in the manufacturing process [12]. Abnormal electroencephalogram patterns

have also been reported in some studies of experimental vitamin B_6 deficiency [49]. Other symptoms associated with severe vitamin B_6 deficiency include hyperirritability, depression, and confusion, hypochromic microcytic anemia, seborrheic dermatitis, cheilosis, glossitis and stomatitis [82]. Nationally representative surveys have shown that the mean intakes of vitamin B_6 of the adult population are between 1.5 and 4.9 mg/day [34, 66, 97], which are well above the intake recommendations set up in various countries. Despite the fact that in general the average dietary intake of vitamin B_6 is high, cross-sectional studies have reported that 16–24% of older adults have poor biochemical vitamin B_6 status [5, 66, 93]. These findings suggest that older adults might have increased requirements for vitamin B_6 intake.

Vitamin B_6 can be found in a variety of animal and plant foods. Particularly rich sources of vitamin B_6 are meat, poultry, fish, legumes and cereals. In contrast to other B vitamins, the absorption of vitamin B_6 in the intestine is through unsaturable passive diffusion. Compared to the bioavailability of the synthetic form of the vitamin, pyridoxine hydrochloride (assumed to be almost 100%), the average bioavailability of vitamin B_6 from a mixed diet was found to be around 75% [88]. However, a considerable proportion of vitamin B_6 in some plant foods (grains, legumes, potatoes, vegetables, oranges) is in the form of pyridoxine glucosides (PNG), which has been reported to have incomplete bioavailability [48]. Studies using stable isotopes in young adults reported that the bioavailability of PNG was around 50% of that of the synthetic vitamin [31, 67]. These results were also in agreement with the findings of a strictly controlled metabolic study which showed that vitamin B_6 status biomarkers were significantly lower in women maintained for 18 days on a diet containing 27% PNG compared with those in women receiving the same amount of vitamin B_6 but through a diet containing only 9% PNG [32]. Therefore, a more sustainable diet which would be based primarily on plant foods would be expected to affect vitamin B_6 status unfavorably, especially in some vulnerable groups of the population (e.g. older adults). However, this problem could be avoided by a proper selection and combination of a variety of plant food choices from different food groups, which would provide sufficient amounts of available vitamin B_6. In support of this view are the results from a cross-sectional study which showed that there was no significant difference in the vitamin B_6 status of vegans, vegetarians and the omnivorous who have followed their diets for more than a year [61].

12.6 Folate

12.6.1 Folate and Folic Acid

Elsewhere, Chap. 29 has considered the role of fortified foods in providing a sustainable source of this important B-vitamin and contributing to optimal nutritional status and better health outcomes for populations worldwide.

The terms folic acid and folate are often used interchangeably by scientists, health professionals and others to describe this B-vitamin. There are, however, important differences. Folic acid refers to the synthetic form of the B-vitamin known as folate as found in fortified foods and supplements, whereas 'folates' are the natural vitamin forms found in plant and animal and human tissues. There are structural differences between the two forms which have important consequences for the bioavailability of folates in the human diet. Folic acid is inherently more stable and bioavailable compared with an equivalent amount of the vitamin eaten as naturally occurring food folates. As described below from a global health point of view, folic acid can provide a sustainable form of the vitamin; this is not achievable through natural food folates.

Metabolically, folate is required for one-carbon metabolism [84]. This metabolism refers to reactions in which folate functions to donate or accept a one-carbon unit in essential pathways involving DNA and RNA biosynthesis, amino acid metabolism and numerous methylation reactions, including DNA methylation. Folate is therefore essential for cell division and tissue growth, and plays a particularly important role in early fetal development. To be metabolically active, folate needs to be in the reduced form of tetrahydrofolate (THF). Biologically active folates exist in various THF forms, but the most predominant form in cells and circulating in plasma is 5 methylTHF.

Other B-vitamins are required to sustain normal folate recycling and thus are also involved in one-carbon metabolism, namely vitamins B_{12}, B_6 and B_2 (i.e. riboflavin) [3]. Deficiency or low status of one of more of the related B-vitamins, or genetic polymorphisms in folate genes, can impair folate metabolism and cause adverse health outcomes (including hypertension owing to a novel folate-riboflavin interaction [89]. Such adverse effects can arise even if folate intakes are deemed to be adequate for a general population. In this way, sustaining optimal status of the related B-vitamins is essential for normal folate metabolism.

Folate deficiency leads to megaloblastic anemia, characterized by larger than normal red cell precursors (megaloblasts) in bone marrow, macrocytes in the peripheral blood and giantism in the morphology of proliferating cells. Biomarker status of folate is routinely assessed by measurement of folate concentrations in serum/plasma or in red blood cells [3]. Red blood cell (RBC) folate is considered the best index of longer-term status (i.e. over the previous months), while serum folate reflects more recent dietary intake. The measurement of plasma total homocysteine concentration provides a reliable functional marker of folate status, on the basis that normal homocysteine metabolism requires an adequate supply of folate. When folate status is low or deficient, plasma homocysteine is invariably found to be elevated.

Dietary folate intakes can be considered suboptimal in the diets of many people in that, although they may be adequate in preventing clinical deficiency (i.e. megaloblastic anemia), they are often insufficient to achieve a biomarker status of folate that is associated with optimal health [3]. This widespread under-provision of folate is generally attributed to the poor stability and incomplete bioavailability of

natural food folates when compared with the synthetic vitamin folic acid (see below).

Other causes of folate depletion relate to higher requirements [3]. Pregnancy is a time when folate requirement is greatly increased in order to sustain the demand for rapid cell replication and growth of fetal, placental and maternal tissue. Likewise, folate requirement is increased during lactation in order to meet maternal and neonatal folate needs. Folate deficiency is also commonly reported in children with sickle cell disease. Folate deficiency is common in chronic alcoholism, which causes intestinal folate malabsorption, decreased hepatic uptake and increased urinary folate excretion. Several commonly used drugs are linked with folate deficiency through various mechanisms. These include: anticonvulsant drugs e.g. phenytoin, primidone; sulfasalazine (for treating inflammatory bowel disease); pyrimethamine (an antimalarial); triamterene (a diuretic); and metformin (used in type 2 diabetes). Methotrexate is a folate antagonist used in the treatment of cancer, rheumatoid arthritis and psoriasis; supplementation with folic acid (or folinic acid) can reduce antifolate toxicity and severe folate deficiency in treated patients.

The richest sources of naturally occurring food folates are green leafy vegetables, asparagus, beans, legumes, liver and yeast [3]. Folic acid, on the other hand, is found in the human diet only in fortified foods and supplements. It is a yellow-orange crystalline solid, tasteless, odorless and moderately soluble in pure water. Folic acid is readily converted to metabolically active folates after it is ingested. Folic acid is fully oxidized and is a monoglutamate, whereas natural food folates are a mixture of reduced folate forms and are typically found in the polyglutamate form. These structural differences between natural folates and folic acid have important consequences for the bioavailability of folates in the human diet.

The intestinal absorption of food folates is a two-step process which involves the hydrolysis of folate polyglutamates to the corresponding monoglutamyl derivatives, followed by their transport through the intestinal membranes into the enterocyte [58]. For various reasons, however, the bioavailability of naturally occurring folates is inherently limited and variable. Apart from their poor bioavailability, natural folates in foods can undergo significant losses before ingestion. Food folates (particularly green vegetables) can be unstable under certain conditions of cooking, and this can substantially reduce the folate content of the food before it is even ingested [57]. The instability and poor bioavailability of natural food folates greatly limits the extent to which optimal folate status can be achieved through intervention with food folate sources alone [20].

Folic acid is inherently more stable and bioavailable compared with an equivalent amount of the vitamin eaten as naturally occurring food folates. The bioavailability of folic acid is assumed to be 100% when ingested as a supplement, while folic acid in fortified food is estimated to have about 85% the bioavailability of supplemental folic acid [44].

In the US and certain other countries, folate recommendations are expressed as Dietary Folate Equivalents (DFEs), which takes into account differences in bioavailability between synthetic folic acid in fortified foods and naturally occurring dietary folate [44]. DFEs are defined as the micrograms of naturally occurring

food folate plus 1.7 times the micrograms of folic acid from fortified food. The IOM [44] recommends 400 μg/day as DFE for adult females and males. To cover increased needs during pregnancy and lactation, it recommends 600 and 500 μg/day respectively.

Although a recent EFSA report has for the first time expressed folate recommendations as DFEs [24], in most European countries this conversion factor is not applied and the differences in bioavailability between the natural food forms and folic acid are disregarded: folate intakes and recommendations are expressed simply as total folate in μg/day rather than as DFEs [37]. Folate recommendations (total folate in μg/day) vary between 200 and 400 μg/day for adults in different European countries. Generally, those countries with more recently generated recommendations based on newer evidence estimate higher folate requirements than those countries (including the UK) with older recommendations still in place.

The UL refers only to folic acid intakes (the synthetic vitamin). No adverse effects have been associated with the consumption of excess folate from foods; therefore, there is no UL for naturally occurring food folates. ULs for folic acid have been set for the US [44], Australia/New Zealand, Europe [24], and for a number of specific European countries: the Nordic and DACH countries, France and The Netherlands. In the US, the IOM [44], estimated a UL for adults (≥ 19 years) for folic acid at 1000 μg/day.

Folate has important impacts on health. Conclusive evidence shows that folic acid supplementation in early pregnancy protects against neural tube defects (NTD)—major malformations in which there is a failure of the neural tube to close properly between the third and fourth week post conception. Although the preventive effect of folate in NTD is the major focus of public health efforts worldwide, folate has other roles in human health which extend throughout the lifecycle from conception to old age, including potential preventative effects against cardiovascular disease, cancer, cognitive dysfunction and osteoporosis [59].

Low and deficient folate status is a global problem which is not confined to developing countries [3]. One extensive review of folate deficiency worldwide assessed population-based surveys of folate status published between 1995 and 2005, including those which included biomarker data [56]. Folate deficiency was identified in specific age-groups in six out of eight countries for which biomarker data existed, most notably in pregnant women in Costa Rica (48.8%) and Venezuela (25.5%), preschool children in Venezuela (33.8%), and the elderly in the United Kingdom (15.0%).

The widespread under-provision of folate that exists in the diets of many people worldwide needs to be addressed. Because of the instability and relatively poor bioavailability of folates from natural sources, enhancing folate intake through plant or animal food sources will not lead to increased status. Folic acid is inherently more stable and bioavailable compared to an equivalent amount of the vitamin eaten as naturally occurring food folates. It is also cheap to produce. As reviewed elsewhere (Chap. 29), folic acid fortified foods can provide a sustainable form of this important B-vitamin and contribute greatly to achieving optimal folate status in populations globally. Folate's role in human health extends throughout the lifecycle

from conception to old age, and fortification of food with folic acid is associated not only with better health outcomes for women of reproductive age but also for other sub-groups. Achieving optimal folate status should be an important public health goal for populations worldwide.

12.7 Vitamin B_{12}

Vitamin B_{12} is the generic term for a group of cobalt-containing compounds known as cobalamins. There are a number of different forms of the vitamin: methylcobalamin and deoxyadenosylcobalamin are the two metabolically active forms, while cyanocobalamin is the synthetic form of the vitamin used in supplements and fortified foods. Vitamin B_{12} is required as a cofactor for two mammalian enzymes, methionine synthase and methylmalonyl CoA mutase. Adenosylcobalamin acts as a co-factor for the latter enzyme which converts methylmalonyl CoA to succinyl CoA, a metabolite in the tricarboxylic acid cycle. This is an important reaction in the metabolism of branched-chain amino acids and odd-chain length fatty acids [83]. Methylcobalamin acts as a co-factor for the enzyme methionine synthase, which catalyzes the re-methylation of homocysteine to methionine, the precursor of S-adenosylmethionine. S-adenosylmethionine is a universal methyl donor essential for the methylation of phospholipids, neurotransmitters, amines, DNA, RNA and myelin basic protein [83]. Clinical signs of vitamin B_{12} deficiency include megaloblastic anemia (as a result of impaired DNA synthesis) and irreversible neurological dysfunction such as sub-acute combined degeneration of the spinal cord [87]. Sub-optimal vitamin B_{12} status characterized by metabolic evidence of deficiency—such as low serum total B_{12} and serum holotranscobalamin and elevated serum methymalonic acid and plasma homocysteine, but without overt signs of clinical deficiency—has also been associated with a number of age-related diseases, including cardiovascular disease [76], cognitive dysfunction [21], dementia [39] and osteoporosis [89].

Vitamin B_{12} is synthesized by microorganisms and is predominately found in foods of an animal origin such as meat, poultry and dairy products or in foods fortified with B_{12} [86]. Currently, inadequate dietary intake of vitamin B_{12} is not a major concern as intakes greatly exceed recommendations (which range between 1.0 and 2.8 μg/day worldwide), except among those that have very low intakes of animal-based foods [43]. There is a high prevalence of vitamin B_{12} deficiency among strict vegetarians and vegans [72], and low vitamin B_{12} is also more common in lower-income countries, where the consumption of animal foods is limited [2]. Therefore, the adoption of a more sustainable plant-based diet would have an unfavorable impact on vitamin B_{12} status, leading to an increase in the prevalence of vitamin B_{12} deficiency among the general population, a problem that at present is largely confined to older adults with malabsorption [43]. A few plant

sources of vitamin B_{12} have been identified; however, they do not offer a viable alternative to animal-based foods, especially in the long term. Certain wild mushrooms contain vitamin B_{12} but would need to be ingested in such large quantities that they do not represent a feasible replacement food source [98]. Furthermore, two forms of edible algae (*Enteromorpha* sp. and *Porphyria* sp.) have been identified as sources of vitamin B_{12}; however, consumption of these products is not widespread within the Western diet [98]. Fortification of foods with vitamin B_{12} offers a viable alternative, but the effectiveness of this strategy will depend on the level of fortification introduced: levels of vitamin B_{12} currently used by the food industry in voluntary fortification are too low to improve status in the general population and need be increased [40]. Vitamin B_{12} food fortification would not only reduce the risk of inadequate intake but also address the issue of food-bound malabsorption, the most common cause of vitamin B_{12} deficiency [43].

12.8 Choline

Choline is involved in various biological reactions including one-carbon metabolism through its metabolite betaine, and the synthesis of the neurotransmitter acetylcholine and phospholipids such as phosphatidylcholine [107]. Deficiency of choline is rare, as it is found in both animal and plant-based foods, but manifests predominantly as fatty liver and impaired liver and muscle function [14, 26, 107]. More recently, studies have focused on the role of choline in pregnancy for neurodevelopment and prevention of neural tube defects, and in later life for reducing the risk of chronic diseases such as cancer, CVD and dementia [37, 91, 107]. Choline can be synthesized endogenously, but intake from food is required to meet current recommendations. An adequate intake (AI) level of 550 mg/day for men and 425 mg/day for women was set, with higher intakes of 450 and 550 mg/day established for pregnancy and lactation respectively [44].

Choline is found in food predominantly as phosphatidylcholine, a lipid-soluble compound, although-water soluble compounds (i.e. free choline, glycerophosphocholine and phosphocholine) are also present [17]. The choline content of many foods, however, only became available in the last decade [42, 71], enabling choline intake to be estimated. Observational cohort studies from the US [10, 17, 106] and from elsewhere [19, 22, 60] consistently report that median intakes are below recommendations, with only a small proportion of people having intakes that meet the AI. The contribution to total choline intake of different food sources varies between studies, but the main food sources reported tend to be foods of animal origin such as eggs, meat and milk, as choline is predominantly present in food as a lipid-soluble compound [9, 17, 18, 22, 68, 106]. Non-animal-based foods such as broccoli and other vegetables, fruit, legumes and bread make a smaller contribution to total intakes, with values of up to 10% reported [17, 18, 68, 106]. A study by

Mygind et al. [68] found, however, that combining foods such as fruit and bread led to a similar contribution to total choline intake as found for red meat. The Attica study in Greece reported that those people who had higher choline intakes consumed more red meat, fruit, vegetables and legumes [22]. In Taiwanese populations, soybean and soy products are found to be an important source of choline, contributing 6% to total intakes [19]. Lewis et al. [50] found that a daily serving of pulses can provide more choline than foods of animal origin, the richest sources typically reported in studies. A daily serving was calculated to provide 15% of the dietary recommendation for choline [50].

As choline is widely present in foods, achieving recommendations should not be an issue as long as a varied diet is consumed. The emergence of further food composition data for choline will enable intake from non-animal food sources to be more accurately calculated. These food sources, however, may differ in pathways of absorption and metabolism to animal sources [17, 18]; therefore, further research is required to determine whether the various forms of choline present in food differ in bioavailability in order to fully understand whether requirements for choline can be met through non-meat food sources.

12.9 Biotin

The water-soluble B-vitamin, biotin, is a bicyclic compound, which acts as a cofactor for five carboxylase enzymes which are important in fatty acid metabolism and in mitochondrial carbohydrate, lipid and amino acid metabolism. Biotin also has a role in gene regulation and genome stability [85]. Although biotin plays a central role in metabolic processes, frank, symptomatic biotin deficiency is a rare occurrence and has been observed only in intravenous feeding without biotin supplementation, and after raw egg-white feeding [64]. Deficiency symptoms include skin rashes, hair loss and neurological symptoms such as depression, lethargy and paresthesia [62]. Recent work, however, indicates that sub-optimal biotin status might be a problem in pregnancy [73]. Perry and co-workers found significant alterations in biomarkers of biotin metabolism in pregnant women and suggested that biotin intakes greatly exceeding current recommendations (Adequate Intake, AI: 30 μg biotin/day) are needed during pregnancy.

Biotin seems to be widely distributed in foods, and particularly rich sources include nuts, egg yolk, liver, dairy products, and some fruit and vegetables (e.g. bananas, avocados, raspberries, cabbage). The biotin content, however, of most foods has not been determined, nor has bioavailability [70]. A specific biotinidase appears to cleave protein-bound biotin in the intestine. ‘Egg-white injury’ is caused by tight binding of biotin by ovidin in raw egg-white. Dietary ovidin can prevent the absorption of dietary biotin and any biotin synthesized by intestinal bacteria.

The effect toward improving sustainability on biotin intakes and status will remain unclear until more is known on the biotin content of foods and dietary requirements, especially during pregnancy.

12.10 Pantothenic Acid

Pantothenic acid has an important role in energy-yielding metabolism as a vital component in the synthesis and maintenance of the cofactor coenzyme A and acyl carrier protein in the fatty acid synthase complex. Clinical symptoms of deficiency have only been observed in people who were fed diets low in, or devoid of, pantothenic acid [27] or fed w-methyl pantothenic acid, an antagonist of the vitamin [35]. The clinical symptoms observed in these experiments were wide-ranging, and included neuromotor disorders, mental depression, gastrointestinal effects, and various metabolic disturbances.

Pantothenic acid is widely distributed in all foodstuffs, and there is little information on bioavailability. Non-nutritional, pharmacological uses of pantothenic acid at doses much higher than the usual 3–7 mg/day (AI) have been proposed, and some efficacy has been demonstrated for acne [104, 105]. Problems with pantothenic acid status are unlikely, whether or not sustainability scenarios are implemented.

12.11 Summary: Key Messages

- It is likely that future scenarios will see trends toward a reduced consumption of animal-based foods and increased consumption of fruit and vegetables.
- Trends towards improving environmental sustainability could impact on B-vitamin status.

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