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Increased Micronutrient Requirements during Physiologically Demanding Situations: Review of the Current Evidence

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Abstract

Every day, the human body is exposed to physical and psychological challenges that upset its internal equilibrium. Strenuous activities, daily defense against pathogens or the response to infection, seasonal changes, and recurring natural biological processes (e.g., the menstrual cycle) can all disturb homeostasis. The body brings its internal environment back into balance by the constant interaction of its many regulatory processes, allowing it to adapt to the ever-changing environment. This ability to adapt and respond (referred to as 'phenotypic flexibility') is fundamental to maintaining good health. Micronutrients (vitamins and minerals) have key roles in numerous homeostatic processes, enabling the body to produce enzymes, hormones and other substances that are essential for energy production, cell maintenance and repair, immune function and recovery from illness, blood formation, and maintenance of vital organs. Micronutrients are thus crucial to facilitate adequate responses to stressors that may challenge the body's homeostasis. Micronutrients are generally not produced by the human body, necessitating an adequate daily intake at levels that have been recommended by various governing bodies. However, micronutrient requirements to optimally support homeostasis during daily demanding situations have not been clearly established. This review examines the roles of micronutrients during some of these demanding situations, to help determine whether there may be a rationale for increasing micronutrient intake during these periods to address any increased needs and potentially aid recovery.

Keywords: Micronutrients; Vitamins; Minerals; Homeostasis; Energy; Immune function; Recovery

Introduction

Homeostasis within the body is a dynamic condition in which the body's equilibrium can shift in response to changing and often demanding conditions, modulated by the constant interaction of the body's many regulatory processes. Homeostasis is continuously being disturbed by physical and psychological stresses, from the demands of work and school or running to catch a bus in time, intense physical exercise, seasonal exposure to temperature or climate extremes, or exposure to bacteria or viruses causing an immune challenge. In most cases, the disruption of homeostasis is mild and temporary and quickly restored by the responses of body cells, but in some cases the disruption may be intense and prolonged. The internal environment of the body is usually brought back into balance by its regulating systems, thus allowing the body to adapt to the ever-changing environment. This ability to respond to a physiological challenge (recently termed 'phenotypic flexibility') is essential to maintaining good health and may be a good indicator of health status [1].

Micronutrients have key roles in numerous homeostatic processes including, for example, those regulating energy metabolism, redox systems, inflammatory responses and immune function [2-4]. Inadequate functioning of these processes reduces the phenotypic resilience to daily challenges, with potential detrimental effects on health [1]. It is well-established that chronic and severe micronutrient deficiencies can increase the risk of poor growth, cognitive development, morbidity, and ultimately mortality [1]. However, the health implications of marginal nutritional inadequacies that may occur when the body is in demanding 'everyday' situations or life stages are less established, largely due to a lack of clear clinical indicators or measures that may point towards a suboptimal nutritional status. Essential micronutrients facilitate adequate responses to stressors that may challenge the body's homeostasis via their impact on immune function or energy production, for example, and thus help to maintain homeostasis [2,5]. Inadequate functioning of these homeostatic processes may reduce phenotypic flexibility, initially leading to common symptoms such as tiredness, fatigue, and an impaired immune response [6-8]. In the longer term, this may lead to a potentially increased risk of chronic disease [1]. Certain situations can place the body under additional stress, for example when it is exposed to pathogens or succumbs to infection, when extra energy is required during and after strenuous activities, when seasonal changes affect our behavior, or when recurring natural biological processes place the body under extra demand, such as during the monthly female reproductive cycle. In each of these situations, micronutrients play a central role in supporting the biological processes that help maintain and restore homeostasis [1-5] (Figure 1).

Therefore, it is of paramount importance to ensure micronutrient intake is sufficient to account for the increased needs or losses associated with these demanding situations. Individuals that are often exposed to increased physiological demands and that don't adapt their micronutrient intakes accordingly may be at increased risk of suboptimal nutritional status, ultimately leading to an impaired health status. This review will provide a detailed overview on the specific micronutrient needs associated with many of these physiologically demanding situations.

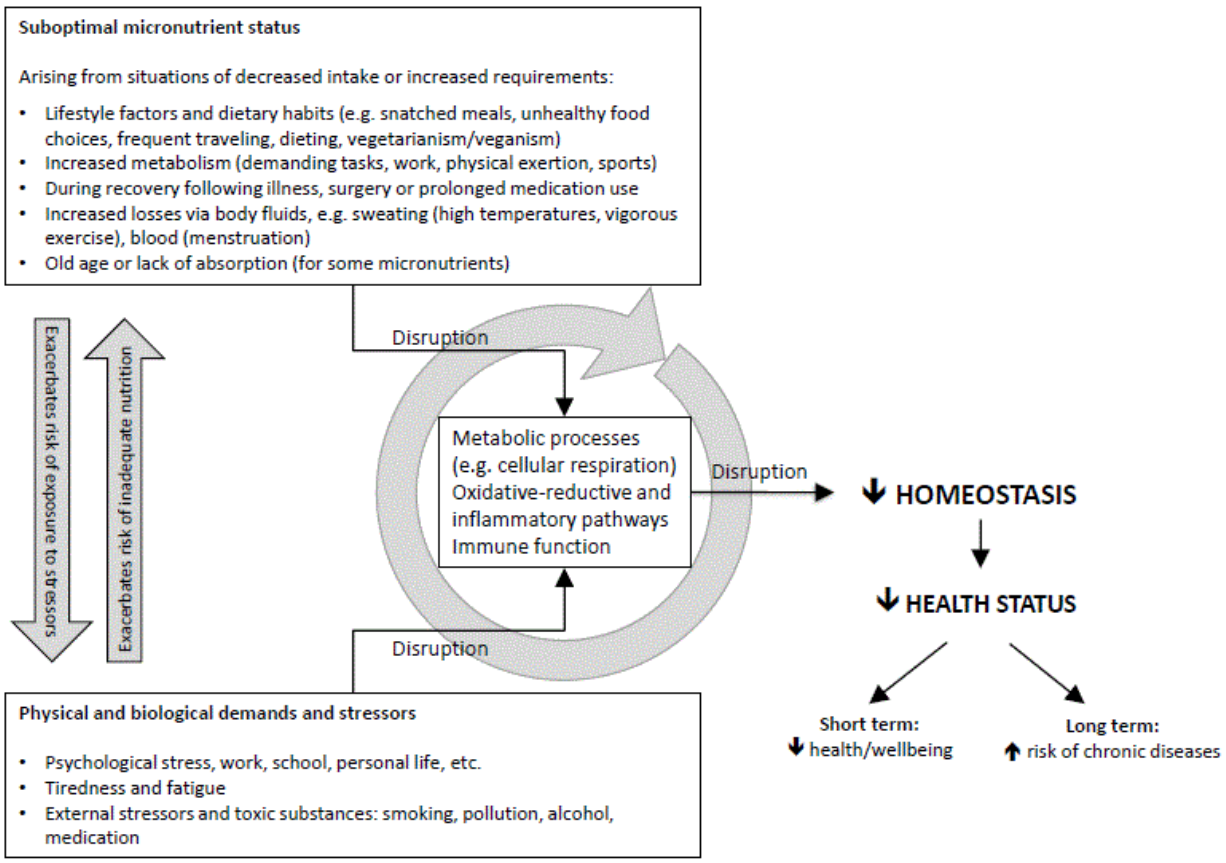

Figure 1: A suboptimal micronutrient status can affect homeostatic processes that are essential to maintaining good health.

Micronutrients are essential for body functions

Micronutrients are vitamins and minerals that are required in miniscule amounts by the body, but which are involved in virtually all metabolic and developmental processes (Table 1).

Vitamins are organic nutrients that generally cannot be synthesized by the body (although some are produced by bacteria in the gastrointestinal tract), and should be ingested daily. Water-soluble vitamins (the B vitamins and vitamin C) are absorbed with water in the gastrointestinal tract and travel freely throughout the body; for the most part, they do not have specific storage sites in the body and are readily excreted once the renal threshold is exceeded. The body therefore needs to be frequently resupplied with water-soluble vitamins. Fat-soluble vitamins (vitamin A, D, E, and K) are absorbed along with other dietary lipids by the small intestine, may be stored in cells, and are not as easily excreted as water-soluble vitamins. Minerals (e.g., calcium, magnesium, zinc, etc.) are inorganic substances that cannot be made by the body and should also be supplied on a frequent basis. They are stored mainly in teeth and bones, in the liver, skeletal muscle, and other tissues. Concentrations of many of the minerals (e.g., calcium) are tightly controlled; when plasma levels are low, the minerals are mobilized from the reserves.

Micronutrients perform a variety of functions that are essential to homeostasis. They enable the body to produce enzymes, hormones and other substances that are required for energy production (e.g., in mitochondrial function), cell maintenance and repair (including division, replication, and growth), immune function and recovery from illness, blood formation, and maintenance and function of the brain, heart, lung, skin, bone, muscle, etc., Vitamins are key to the regulation and coordination of these homeostatic processes, mostly acting as coenzymes (as do minerals such as zinc) or hormones (e.g., vitamins A and D). Vitamins are essential to bone health [9], wound healing [10], the function, development and differentiation of the immune system [11-13], and microsomal drug metabolism and detoxification [14].

Apart from the established consequences of chronic vitamin deficiency (e.g., neural tube defects in pregnancy with folate deficiency, pernicious anaemia with low vitamin B12 or folate status, rickets or osteomalacia with vitamin D or calcium deficiency, etc.), a growing body of evidence is beginning to demonstrate the importance of an adequate vitamin status in the maintenance of good health and in the prevention of diseases [1,15,16]. In their ionized form, essential minerals (e.g., calcium, iron, zinc, magnesium, selenium, etc.) have functions that are vital to life. They are structural components of enzymes, neuropeptides, hormones and hormone receptors, with various roles in numerous enzymatic and metabolic reactions, nerve transmission, and maintaining the structure of bones and teeth [17]. Table 1 provides an outline of some of the main roles of essential micronutrients, where they can be sourced, and their storage within the body [7,11,18].

Main roles in the body		Sources and storage
Vitamins		
Fat soluble (all require bile salts and some dietary lipids for adequate absorption)		
A (formed from provitamin beta-carotene, and other provitamins)	Maintains general health of epithelial cells, maintaining innate barriers; acts as an antioxidant to inactivate free radicals; essential for formation of photopigments (light-sensitive chemicals in photoreceptors of retina); aids in growth of bones and teeth; important for innate, cell-mediated immunity and antibody response	Yellow and green vegetables (beta-carotene), liver and milk (vitamin A). Stored in liver (approx. 900 mg)
D	Essential for absorption and utilization of calcium and phosphorus from the gastrointestinal tract; works with parathyroid hormone to maintain calcium homeostasis; the active form of vitamin D, calcitriol (1,25-dihydroxcalciferol) is a potent immunomodulator, involved in cell proliferation, innate and adaptive immunity	Sunlight is usually adequate; fish-liver oils, egg yolk, fortified milk. Excess stored in fatty tissues to a slight extent
E (tocopherols)	Thought to inhibit catabolism of certain fatty acids that help form cell structure, especially membranes; aids innate immunity by maintaining epithelial barriers; involved in formation of DNA, RNA and red blood cells; may promote wound healing, contribute to the normal structure and functioning of the nervous system, and prevent scarring; believed to help protect liver from toxic chemicals; potent chain-breaking, lipid-soluble antioxidant that inactivates free radicals and protects cell membranes	Fresh nuts, wheat germ, seed oils, green leafy vegetables. Substantial stores in liver, fatty tissue, and muscles
K	Coenzyme essential for the synthesis of several clotting factors by the liver, including prothrombin	Produced by intestinal bacteria; spinach, cauliflower, cabbage, liver. Stored in liver and spleen
Water soluble (absorbed along with water in the gastrointestinal tract and dissolved in body fluids)		
B1 (thiamine)	Acts as a coenzyme for many different enzymes, involved in metabolism of carbohydrate to energy; essential for synthesis of the neurotransmitter acetylcholine; needed for normal muscle function	Whole-grain products, eggs, pork, nuts, liver, yeast. Relatively high turnover means there are low reserves in various tissues (approx. 25-30 mg)
B2 (riboflavin)	Component of certain coenzymes in carbohydrate and protein metabolism (especially in eye cells, integument, intestinal mucosa, blood); helps release energy from food	Bacteria of gastrointestinal tract, yeast, liver, beef, veal, lamb, eggs, whole-grain products, asparagus, peas, beets, peanuts. Stored in small amounts in the liver, spleen, and kidneys
B3 (niacin)	Essential component of a coenzyme found in all living cells, involved in oxidation-reduction reactions; inhibits production of cholesterol, assists in triglyceride breakdown; helps release energy from food	Derived from amino acid tryptophan; yeast, meats, liver, fish, whole-grain products, peas, beans, nuts. Small amounts stored in the liver
B5 (pantothenic acid)	The precursor of coenzyme A (essential in the citric acid cycle, conversion of lipids and amino acids into glucose, and synthesis of cholesterol and steroid hormones)	Some produced by bacteria of gastrointestinal tract; kidneys, liver, yeast, green vegetables, cereal. Stored primarily in the liver and kidneys
B6 (pyridoxine)	Essential coenzyme for normal amino acid metabolism; assists circulating antibody production; may function as coenzyme in triglyceride metabolism; helps release energy from food; modulates cellular immunity through involvement in nucleic acid and protein biosynthesis	Synthesized by bacteria of gastrointestinal tract; salmon, yeast, tomatoes, yellow corn, spinach, whole-grain products, liver, yoghurt. Mostly stored in muscle (but also the liver and brain) (approx. 40-250 mg) - but not readily available
B7 (biotin)	Essential coenzyme for conversion of pyruvic acid to oxaloacetic acid and synthesis of fatty acids and purines, and utilization of B vitamins	Synthesized by bacteria of gastrointestinal tract; yeast, liver, egg yolk, kidneys
B12 (cobalamin)	Coenzyme necessary for red blood cell formation, formation of amino acid methionine, entrance of some amino acids into the citric acid cycle, manufacture of choline (used to synthesize acetylcholine); essential for metabolism of fats and carbohydrates and the synthesis of proteins; interacts with folic acid metabolism; modulates cellular immunity through involvement in nucleic acid and protein biosynthesis, aids in antibody production	Only B vitamin not found in vegetables; liver, kidney, milk, eggs, cheese, meat. Approx. 3-5 mg is stored, mostly (80%) in the liver
B9 Folate	Component of enzyme systems essential for DNA and RNA; essential for normal production of red and white blood cells; essential metabolic pathways involving cell growth, replication, survival of cells; modulates cellular immunity through involvement in nucleic acid and protein biosynthesis, aids in antibody production	Synthesized by bacteria of gastrointestinal tract; green leafy vegetables, liver. Approx. 5-10 mg is stored, 50% in the liver (represents at least 2 months' supply)
Minerals		

Calcium	Formation of bones and teeth, normal muscle and nerve activity, endocytosis and exocytosis, cellular motility, chromosome movement prior to cell division, glycogen metabolism, synthesis and release of neurotransmitters	Milk, egg yolk, shellfish, green leafy vegetables. Vitamin D is necessary for active absorption of calcium, and has a positive impact on passive absorption [173]. Most abundant mineral in the body; approx. 1.2 kg is stored, 99% in bone and teeth, remainder in muscle, other soft tissues, and blood plasma. Blood calcium levels tightly controlled by calcitonin and parathyroid hormone
Iron	Reversibly binds oxygen as a component of haemoglobin; component of cytochromes involved in electron transport in the respiratory chain; essential component of myoglobin for transporting and storing oxygen in muscle and releasing it when needed during muscle contraction; necessary for red blood cell formation and function	Meat, liver, shellfish, egg yolk, beans, legumes, dried fruits, nuts, cereals. Approx. 4 kg is stored in males and 2.1 kg stored in females; about 60% is found in haemoglobin of blood; remainder in skeletal muscles (myoglobin), liver, spleen, bone marrow
Iodine	Required by the thyroid gland to synthesize thyroid hormones, which regulate the metabolic rate	Seafood, iodized salt, vegetables grown in iodine-rich soils. Approx. 15-20 mg is stored, 80% in the thyroid gland
Potassium	Functions in nerve and muscle action potential conduction	Fruit (e.g., banana, prunes, plums, oranges, raisins) and salad/vegetables (e.g., tomatoes, potatoes, artichokes). Stored mostly within muscle cells, the balance is strictly controlled
Magnesium	Required for normal functioning of muscle and nervous tissue; participates in bone formation; constituent of many coenzymes, particularly those involving metabolism of food components; required by all enzymatic reactions involving adenosine triphosphate, the energy storage molecule	Widespread sources, including green leafy vegetables, seafood and whole-grain cereals. Approx. 25 g stored in the body, around 60% in the skeleton, 27% in muscles and the remainder in other cells and tissues.
Zinc	Essential component of certain enzymes, including the copper/zinc -superoxide dismutase (a key enzyme in the defense against reactive oxygen species); important in carbon dioxide metabolism and energy metabolism; necessary for normal growth and wound healing, maintenance of epithelial barrier, normal taste sensations and appetite, normal sperm counts in males, and antibody production; involved in protein digestion	Found in many foods, especially meat. Approx. 2-3 g stored, 60% in skeletal muscles, 30% in bone, 4-6% in skin, and the remainder in cells; not easily mobilized from reserves and regular intake is important
Copper	Required for synthesis of haemoglobin, along with iron; necessary for the function of over 30 proteins; a component of coenzymes in the electron transport chain; part of the copper/zinc -superoxide dismutase (a key enzyme in the defense against reactive oxygen species)	Eggs, whole-wheat flour, beans, beets, liver, fish, spinach, asparagus. Some stored in liver and spleen
Selenium	Acts as an antioxidant, and has a role in cellular immunity and antibody production; prevents chromosome breakage and may play a role in preventing certain birth defects	Seafood, meat, chicken, grain cereals, egg yolk, milk, mushrooms, garlic. Approx. 30 mg is stored, depending on geographical location (selenium can be found in soil, and thus accumulates in plants); found in all tissues, bound to amino acids and proteins; regular intake needed to maintain adequate reserves
Chromium	Potentiates normal activity of insulin in carbohydrate and lipid metabolism, promoting glucose uptake by the cells	Brewer's yeast, wine, some beers
Molybdenum	Biological form is molybdenum cofactor, known to function as a cofactor for four enzymes, particularly sulphite oxidase which is crucial for human health (necessary for the metabolism of sulphur-containing amino acids)	Legumes (beans, lentils peas) are the richest source, grain products and nuts also good sources; content is dependent on soil content, so varies by geographical location

Table 1: Summary of the main roles of vitamins and minerals in the body, their sources and the approximate amounts stored in the body [7,11,18,91,171,172].

Recommended vs. actual daily micronutrient requirements

Clearly, an adequate supply of micronutrients is vital to maintain health. But what does adequate mean? The Institute of Medicine (IOM) [19] provides a set of reference values called dietary reference intakes (DRI) that are used to plan and assess nutrient intakes of healthy people, based on age and gender (Table 2).

These values include the recommended dietary allowance (RDA), which is the average daily level of intake that is deemed sufficient to meet the nutrient requirements of nearly all (97%-98%) healthy people. Other guidelines, usually country specific, provide their own recommendations [20-23]. It should be noted that these values are recommended to avoid deficiency - they often don't give an indication of the optimum levels required (Figure 2).

There is a scarcity of data to define optimum micronutrient intake levels, which ultimately will vary for different individuals and depend on several factors including genetic differences and lifestyle factors, as well as intended benefit or outcome measures.

In the developed world, it is often assumed that the easier availability of fresh, nutritious foods means that our diets will be varied enough to meet daily micronutrient requirements. However, it appears that levels regularly fall short of those that are recommended. For example, although the mean daily intake reported across Europe

was generally within the recommended range [24], the levels reported within each country varied considerably and frequently fell short even of the somewhat conservative levels recommended both within Europe and by the IOM (Table 2).

In particular, it was recognized that reference intake levels for vitamins D and E and folate were not met, and that in most participating countries intakes of calcium, magnesium and iron (women only) were also below recommended levels. Similar findings have been made elsewhere [25,26]. Nutritional status is a complex issue that is dependent on many circumstances related to lifestyle (e.g., level of physical activity, alcohol consumption, vegetarianism/veganism), socioeconomic factors (e.g., poverty/low income, the need to work and/or a hectic, stressful lifestyle, and so an inadequate time for shopping or cooking, an increased consumption of convenient, and often nutritionally-poor food), health (e.g., dieting, medication use), and geographical or mobility factors (e.g., no easy access to nutritious food, areas where food choice is dependent on season).

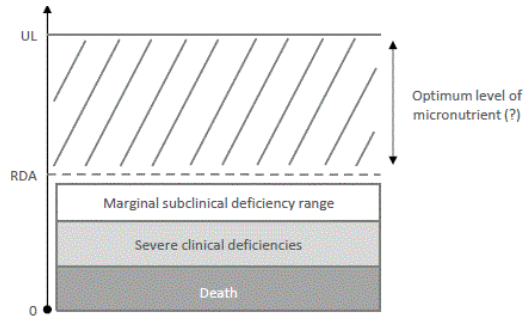

Figure 2: Optimum levels of micronutrients may be much higher than the recommended dietary allowance (RDA) recommended by the Institute of Medicine [19].

	Males				**Females** [a]			
	Recommended daily intake		**Reported mean daily intake in Europe [24]**	**Recommended daily intake achieved**	**Recommended daily intake**		**Reported mean daily intake in Europe [24]**	**Recommended daily intake achieved**
	Europe [b] [24]	USA & Canada [c] [19]			Europe [b] [24]	USA & Canada [c] [19]		
Vitamins								
Fat soluble								
A, mg	1.0	0.9	0.5-2.2	✖	0.8	0.7	0.5-2.0	✖
D, µg	5.0	15-20	1.6-10.9	✖	5	15-20	1.2-10.01	✖
E (tocopherols), mg	13-15	15	3.3-17.4	✖	12	15	4.2-16.1	✖
Water soluble								
B1 (thiamine), g	1.1-1.3	1.2	1.1-2.3	✔	1	1.1	0.9-2.1	✖
B2 (riboflavin), mg	1.3-1.5	1.3	1.4-2.4	✔	1.2	1.1	1.2-2.8	✔
B3 (niacin), mg	15-17	16	9.2-41.3	✖	13	14	6.4-30.6	✖
B6 (pyridoxine), mg	1.5	1.3–1.7	1.6-3.5	✔	1.2	1.3-1.5	1.3-2.1	✔
B12 (cobalamin), µg	3	2.4	1.9-9.3	✖	3	2.4	1.0-8.8	✖
Folate, µg	400	400	203-494	✖	400	400	131-392	✖
C, mg	100	90	64-153	✖	100	75	62-153	✖
Minerals								
Calcium, mg	1000	1000–1200	687-1171	✖	1000	1000–1200	508-1047	✖

Iron, mg	10	8	10.6-26.9	✔	10–15	8–18	8.2-22.2	✖
Iodine, µg	150	150	67-264	✖	150	150	48-200	✖
Potassium, g	2	4.7 [d]	2.7-4.4	✖	2	4.7 [d]	2.3-3.6	✖
Magnesium, mg	350–400	420	256-465	✖	300-310	310-320	192-372	✖
Zinc, mg	10	11	8.6-14.6	✖	7	8	6.7-10.7	✖
Selenium, µg	30–70	55	36-73	✔	30-70	55	31-54	✔

Table 2: Recommended daily intake of vitamins and minerals, compared with mean daily intake reported in Europe [19,24] *. * The amounts of micronutrients that are needed are not an indication of their importance. a. Not pregnant or lactating women; b. aged 19–64 year; c aged 19 to >70 years; d adequate intake (AI), established when evidence is insufficient to develop a recommended dietary allowance (RDA) and is set at a level assumed to ensure nutritional adequacy.

It is well established that inadequate micronutrient intake and status increase the risk of adverse health effects [15,16], with the severity of these health effects largely depending on the extent and the duration of the inadequacy. The next sections will describe in detail the various situations which may increase the risk of suboptimal micronutrient status, ultimately leading to impaired health when not addressed appropriately.

The varying requirements for micronutrients in demanding situations

An inadequate intake of micronutrients is known to result in low energy and fatigue [7,27], and can weaken our immune system and reduce resistance to infections [11,12]. Thus, in everyday life it is essential that we consume sufficient amounts of micronutrients to maintain basic health. Furthermore, optimum micronutrient levels are required in the long term to help prevent chronic diseases such as osteoporosis, coronary heart disease, and cancer [15,16]. Yet for a significant proportion of the population, a gap already exists between micronutrient intakes and minimal requirements and recommended levels are not always achieved [24,25]. This gap is likely to become even wider when our bodies are in demanding situations, leading to additional micronutrient needs. Micronutrients have a fundamental role in so many physiological processes that there is an increased need for certain vitamins and minerals when the body is coping with demanding situations (e.g., related to energy metabolism, immunity, seasonal demands, or during periods of hormonal fluctuations such as the menstrual cycle). A closer look at the role and requirements of micronutrients in such situations can help to evaluate the need for an increased intake of certain micronutrients during these times.

Roles of micronutrients in coping with increased energy demands and combating fatigue: Several micronutrients are required in a number of key reactions during the production and metabolism of energy, which is stored in ATP (adenosine triphosphate), the body's energy storage molecule [6] (Figure 3).

The body's preferred dietary source for synthesizing ATP is glucose, which undergoes a series of reactions mainly in the mitochondria, collectively known as cellular respiration: 1) glycolysis, where glucose is broken down to produce pyruvic acid (and ATP); 2) acetyl coenzyme A (CoA) production, where pyruvic acid is prepared for entrance into the citric acid cycle (also known as Krebs cycle); 3) the citric acid cycle, a set of reactions that oxidize CoA to produce carbon dioxide, ATP, nicotinamide adenine dinucleotide plus hydrogen ($NADH+H^+$) and flavin adenine dinucleotide ($FADH_2$); 4) electron transport chain (ETC) reactions, which oxidize $NADH+H^+$ and $FADH_2$ and transfer their electrons through a series of electron carriers, enabling small amounts of energy to be released to form many molecules of ATP.

During each step of cellular respiration, certain micronutrients play an essential role. In particular, the B vitamins thiamine, niacin, riboflavin and pantothenic acid act as coenzymes and precursors in many cellular functions, and are cofactors in energy production via their role in the citric acid cycle, the ETC and the formation of ATP [7,28]. Thiamine and riboflavin are involved in the citric acid cycle and complexes I and II of the mitochondrial respiratory chain, coenzyme A contains pantothenic acid, biotin is involved in heme biosynthesis (an essential component of the cytochromes involved in the respiratory chain), FAD is derived from riboflavin, vitamin C has a role in the citric acid cycle, converting fat and amino acid to pyruvic acid and thus ATP, iron and sulphur are essential for electron transfer during the ETC, and pyroxidine, cobalamin and folate are necessary to maintain the mitochondrial one-carbon transfer cycles by regulating mitochondrial enzymes [6,28,29]. The importance of micronutrients is clear, and an adequate intake is necessary for optimal energy production.

There are times when we require more energy (e.g., during exercise or other metabolically-demanding tasks such as during physical or even mental work). These increased energy requirements can put us at increased risk of feeling tired and even fatigued. Fatigue, tiredness and low energy are common symptoms in the general population, with a reported prevalence of between 5% and 45% [30,31], and can lead to impaired quality of life and loss of productive work time [30]. Although common causes of tiredness and fatigue include viral illness, upper respiratory infections, iron-deficiency anaemia (for example due to menstrual blood losses), and depression [32], inadequate nutrition also plays a role. Given the importance of micronutrients in energy production and metabolism, it is possible that in the absence of an identifiable underlying disease, an insufficient intake of key micronutrients could cause decreased enzymatic activity, with consequent impaired cellular energy metabolism and an inability to meet metabolic demands, ultimately leading to feelings of tiredness and fatigue [6,7].

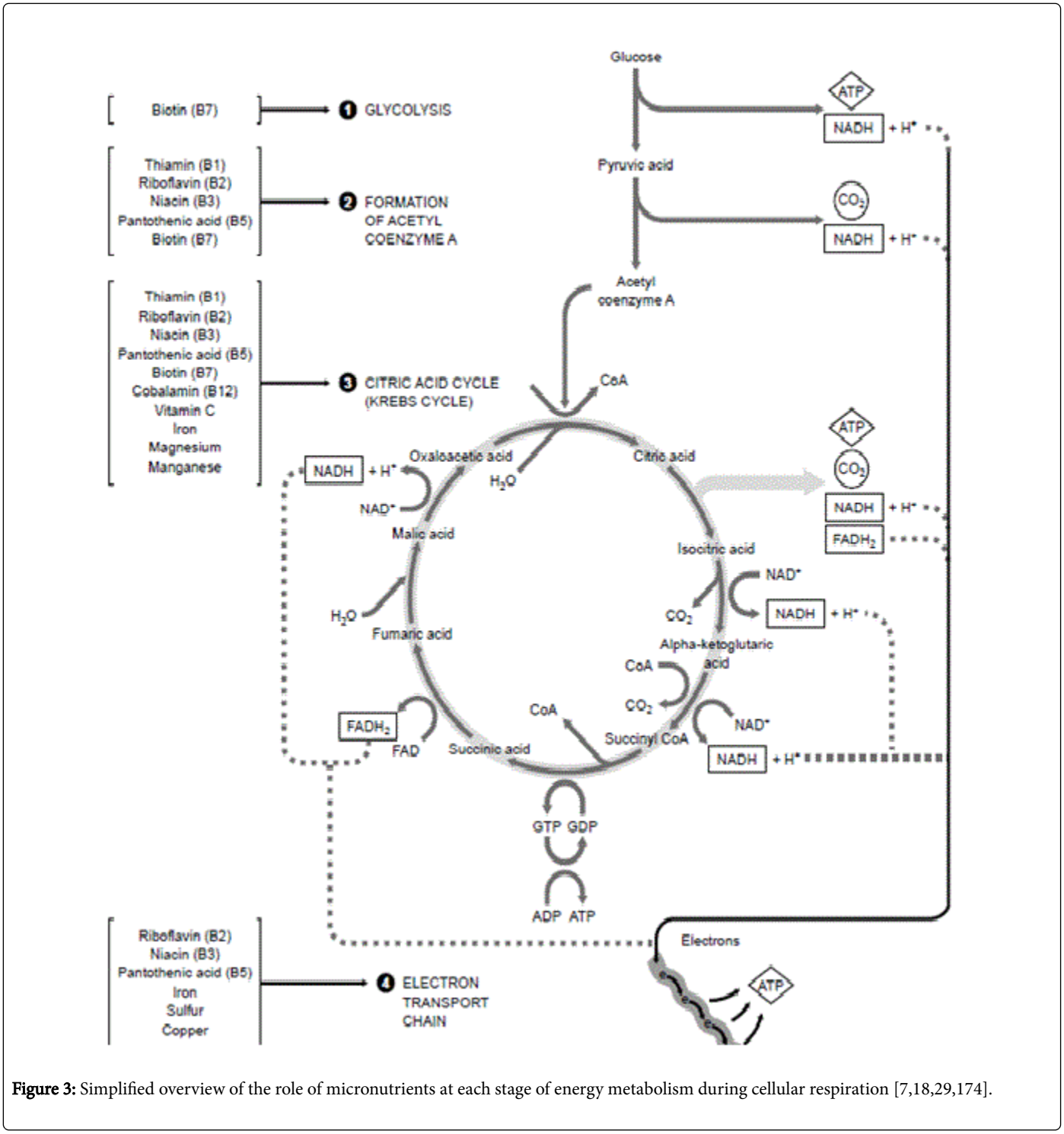

Figure 3: Simplified overview of the role of micronutrients at each stage of energy metabolism during cellular respiration [7,18,29,174].

Increased energy expenditure means that it is necessary for our bodies to produce more energy in the form of ATP, and the demand for micronutrients involved in this process will be greater; more of the body's already limited stores of micronutrients will be utilized unless they can be replenished. In fact, there is some evidence of a shortage of certain vitamins and minerals among active individuals, including the B vitamins, vitamin C, calcium, iron, zinc, and magnesium [33-42]. A suboptimal micronutrient status may affect recovery after activities that cause increased energy expenditure. For example, it has been observed that during periods of low vitamin intake there is a significant 10% decrease in maximal aerobic power - a physiological parameter to quantify the body's capability to uptake, transport and utilize oxygen [43]. A deficiency in vitamin C is associated with impaired folate metabolism, which can lead to fatigue and anaemia [33]. Furthermore, vitamin C depletion is associated with reduced work efficiency during submaximal exercise [44]. The exercise intolerance experienced by some individuals may be related to inadequate vitamin C status due to their lower carnitine levels; vitamin

C is a required cofactor for carnitine synthesis, while carnitine is needed to transport fatty acids into the mitochondria, where they are oxidized to release cellular energy [44]. Calcium deficiency affects both bone density and muscle contraction, both of which are detrimental to physical activity [34,45]. Magnesium deficiency can occur after prolonged heavy exercise, causing muscle weakness and neuromuscular dysfunction [46,47]. This may be a function of both sweat losses and redistribution of serum magnesium into working muscles [34,37,48]. A low zinc intake can result in functional disturbances in energy metabolism [49], and is associated with impaired muscle function, including reduced strength and increased propensity to fatigue, decreased power output during peak work capacity testing, and decreased cardiorespiratory function [38,50-52].

Supplementing with micronutrients may help to boost energy production and increase energy levels [7,27,28]. For example, daily intake of a multivitamin/mineral supplement for two months in healthy adults significantly increased energy production during demanding tasks compared to placebo [28]. An adequate intake of micronutrients is necessary to cover increased needs for building, repair, and maintenance of lean body mass in physically-active people [33,34], thus aiding recovery from exercise or other strenuous activities [45]. There is evidence to suggest there is a need to increase the intake of B-complex vitamins beyond the RDA after exercise [40]. Several studies have investigated the effects of single micronutrients on fatigue, in particular thiamine and iron, as well as supplementation with a combination of these micronutrients. Supplementation with thiamine led to significantly increased wellbeing, decreased fatigue and increased activity in elderly women [53], and to a positive association with feeling clearheaded, composed and more energetic in a young female population [54]. Although the results in the young females didn't quite reach significance (possibly because they may have had an adequate thiamine status before supplementation, while marginal deficiency would be more common in the elderly female population), supplementation with thiamine does still show a trend in combating fatigue in an adequately nourished population. Iron deficiency, even in the absence of anaemia (i.e., a sign of clinical deficiency), is associated with decreased activity of iron-dependent enzymes, and supplementation with iron in non-anaemic women with unexplained fatigue led to a reduction in fatigue, particularly in women with the lowest baseline levels of serum ferritin [55], the most sensitive marker of iron status [56]. Supplementation with multiple micronutrients also has a positive effect on fatigue. For example, a supplement containing vitamin C, B vitamins, calcium and magnesium has been shown to improve fatigue by 82% [57]. Use of a micronutrient supplement for two months in healthy females was shown to reduce fatigue and improve the speed and accuracy of their multi-tasking ability, indicating that multiple micronutrient supplementation may have a beneficial effect on fatigue and can ultimately help in the completion of demanding tasks [58]. In a subgroup of these women, there was also a significant reduction in homocysteine after supplementation [58]. Homocysteine is the potentially toxic amino acid by-product of one-carbon metabolism, and is an indicator of poor health [58]. Vitamins B6 and B12 and folate play an essential role in lowering homocysteine levels, and the fact that homocysteine levels were high in this seemingly healthy population suggests that marginal micronutrient deficiencies commonly occur even in a relatively normal cross-section of healthy females [58]. Another study showed that in healthy people suffering from self-perceived fatigue and vitamin D deficiency, a single high-dose supplement of vitamin D3 significantly improved fatigue, which also correlated with a rise in 25-hydroxyvitamin D levels, the major circulating form of vitamin D [59]. Magnesium supplementation has also been shown to have effects on the economy of respiratory metabolism and exercise tolerance [37,45,50,60-62], while zinc supplementation has been shown to increase muscle endurance [63]; these findings suggest they may have a role in delaying tiredness and fatigue.

Micronutrient supplementation also has potential benefits in sufferers of chronic fatigue syndrome (CFS), a medically unexplained persistent or recurring fatigue lasting at least 6 months [64]. Evidence suggests that oxidative stress plays a pivotal role in CFS, where excess oxidants (reactive oxygen species) are free to attack cell components [65]. These oxidants are normally neutralized by antioxidants such as vitamins C or E, or endogenous antioxidant enzymes such as glutathione peroxidase or superoxide dismutase (which require copper, zinc, and selenium for proper functioning) [3]. It is possible that the illness itself (rather than an inadequate diet) could be causing CFS patients to be marginally deficient in these micronutrients [66]. Consequently, oxidative stress occurs as a result of diminished antioxidant capacity and/or decreased activity of antioxidant enzymes [65]. In CFS patients, multiple micronutrient supplementation significantly reduced fatigue and superoxide dismutase activity (suggesting that antioxidant activity improved with supplementation) [65]. There were also significant improvements in sleep disorders, autonomic nervous system symptoms (e.g., dizziness, anxiety, etc.), frequency and intensity of headaches, and subjective feelings of infection [65]. It has been suggested that it is rational to consider micronutrient supplementation in CFS patients, at least for a trial period [66].

Clearly, micronutrients have essential roles in the homeostatic regulation of physiological processes involved in energy metabolism and ultimately production. To ensure minimal perturbation to homeostasis following increased levels of metabolic stress, as in the case of energy-demanding activities, a sufficient intake of micronutrients is necessary to reduce tiredness and fatigue and aid an adequate response to recovery.

Roles of micronutrients in the recovery from periods of illness: The human immune system is usually well equipped to fend off attacks from pathogens and protect against infection [12,67]. A crucial factor modulating immune function is nutritional status, and essential micronutrients work in synergy in many of the processes involved in the development, maintenance and expression of the immune response. In particular, vitamins A, D, C and E, folic acid, vitamin B6, vitamin B12, zinc, copper, iron, and selenium all contribute to the body's natural defences by supporting physical barriers (skin and mucosa), cellular immunity, and antibody production [11,12].

If nutritional status becomes compromised, immune functions that are fundamental to protect the host from infectious agents such as bacteria and viruses can be suppressed [68, 69]. Pathogens are then more easily able to evade the immune defences, predisposing us to infection and illness. Once the body succumbs to illness, there may be a greater need for micronutrients to support the immune response and allow convalescence. However, during infection the absorption of micronutrients may be impaired, direct micronutrient losses can occur, metabolic requirements or catabolic losses may be increased, and transport of micronutrients to target tissues may be impaired [70]. As a result, there may be a loss of minerals (e.g., potassium), trace elements (e.g., zinc, copper) and vitamins (e.g., vitamins A and B12, folate) [71]. It has been shown that with the onset of infection, serum and plasma levels of calcium, zinc, iron, vitamin A, E and C fall rapidly and return

to normal when symptoms improve [72]. Recovery from infection depends on the intensity of the acute-phase immune response [73]. This is a complex early-defines system activated by trauma, infection, stress, and inflammation, and is the basis of the innate immune response involving physical barriers (skin and mucosa) and responses that serve to prevent infection, clear potential pathogens, initiate inflammatory processes and contribute to recovery and the healing process [72,73]. Micronutrients have essential roles in all of these processes [11,12]. Yet during infection a decrease in food intake can also occur [70], which may prevent effective recovery as deficiencies of specific micronutrients will impair the ability of cells in general and the cells of the immune system in particular to function adequately and effectively [71]. Thus, micronutrient supplementation could be beneficial for the recovery process.

The vitamin that has been studied most regarding a role in managing infection is vitamin C in common cold. Vitamin C is found in high concentrations in leukocytes and is readily mobilized during infection; in fact, it may be defined as a stimulant of leukocyte functions, particularly movement of neutrophils and monocytes [11]. Although its role in antibody production isn't clear, supplementation with vitamin C has been demonstrated to stimulate the immune system by enhancing T-lymphocyte proliferation in response to infection increasing cytokine production and synthesis of immunoglobulins [11]. High supplemental intakes of vitamin C stimulate phagocytic and T-lymphocytic activity [13]. Regular supplementation trials [74], and two controlled trials of high-dose vitamin C supplementation [75], have shown that vitamin C can reduce the severity of cold symptoms and the duration of a cold. Controlled trials have also shown treatment benefits of vitamin C in pneumonia and tetanus patients [75]. Given the consistent effect of vitamin C on the duration and severity of colds in regular supplementation studies, and the low cost and safety, it may be worthwhile for common cold patients to test on an individual basis whether therapeutic vitamin C is beneficial for them [74]. Likewise, zinc lozenges may also shorten the duration of a cold by almost 3 days [76], with the greatest effect for high doses of zinc [77], and improve the recovery rate in common cold patients [78]. There is some evidence to suggest that vitamin E may have the potential to reduce the duration of common cold in elderly patients, but the results were non-significant [79].

Although few clinical studies have evaluated the effects of supplementation with other micronutrients to reduce the severity of an infection such as common cold, there is a rationale for ensuring that micronutrient levels are at least optimal to aid recovery during an infection. For example, vitamin A deficiency suppresses the activity of natural killer cells, eosinophils, macrophages and neutrophils involved in the innate immune responses that help to clear infection, while supplementation appears to reverse these abnormalities [11,13]. Vitamin A deficiency can also impair the antibody-mediated adaptive immune response [12]. Even marginal vitamin B6 deficiency impairs lymphocyte maturation and growth and is associated with decreased numbers and function of T lymphocytes, which can be corrected with short-term supplementation [11,12]. Vitamin B6 also acts as a coenzyme in the metabolism of antibodies, and deficiency is associated with decreased antibody response [11]. Low levels of vitamin B12 lead to a significant reduction in cells that have a role in cell-mediated immunity [11,13]; because vitamin B12 supplementation reverses these effects, it is thought that it may act as a modulatory agent for cellular immunity [17,80]. Vitamin B12 deficiency may also result in an impaired antibody response [11]. Vitamin D modulates the responses of macrophages, preventing them from releasing too many inflammatory cytokines and chemokines, and increasing the 'oxidative burst' potential of macrophages [17,72,81]. Vitamin D deficiency impairs the immune capabilities of macrophages, including their antimicrobial function, effects that can be mitigated by the addition of calcitriol, the hormonally-active metabolite of vitamin D [81].

A final point to consider is the use of antibiotics during severe colds or infections. Antibiotics have a negative effect on the gut microflora [82,83], which may be ameliorated by the use of probiotics [84,85]. They can also deplete certain micronutrients, including folic acid, iron, vitamins D, K, B1, B2, B3, B6 and B12, calcium, magnesium, and potassium [14,86-88]. Several mechanisms may be involved, including a reduction in micronutrient absorption, complex formation, chelation, enzyme induction, mucosal block or damage, and decreased endogenous production [88]. Thus, it is important to ensure that micronutrient intake is sufficient if antibiotics are used during infection, to avoid adverse effects on homeostasis and potentially aid recovery. This is also the case with many other classes of medication that can also have adverse effects on micronutrient status (e.g., some analgesics may reduce iron concentrations, antacids can reduce vitamin D and folate, while certain hypertensive agents lead to a reduction in vitamin B6) [14,86,87]. In the context of medications affecting micronutrient status, it should also be mentioned that various nutritional components can affect each other via interactions e.g., in the gastrointestinal tract, especially among the minerals: For instance, interactions of nutritional significance include sodium-potassium, calcium-magnesium, manganese-iron, iron-copper, and zinc-copper [89]. However, these interactions often depend on the level of mineral administered with only large amounts administered over longer periods of time impairing nutrient status. For example, most human studies investigating effects of dietary calcium on magnesium absorption have shown no negative effect. Only intakes of calcium in excess of 2,600 mg/day have been reported to decrease magnesium balance [90]. Similarly, only large quantities of zinc (>50 mg/d) over a period of weeks have been shown to interfere with copper bioavailability and ultimately status [91]. It is therefore important to keep track of the levels of minerals ingested over longer time periods.

Seasonal demands on the body: Throughout the year, the temperature and climate in many countries can fluctuate considerably. In the heat of the summer, our bodies may sweat more during thermoregulation and we tend to eat lighter, smaller meals. During the winter, adverse weather means that more time is spent indoors, light levels are lower, and colds and flu are more common. These seasonal variations can place additional demand on the body and have an impact on micronutrient needs.

Winter: During the winter months, the human body is placed under several kinds of stress. For example, most people should be able to get all the vitamin D they need from sunlight, synthesized in the skin from 7-dehydrochlesterol by UV-B radiation. But the effectiveness of vitamin D production is dependent on the intensity and duration of sunlight to which the skin is exposed. Consequently, most people produce less vitamin D during the darker, winter months when not only is there a low ambient UV radiation level, but we spend more time indoors; in some cooler climates, vitamin D synthesis can even cease [92]. Yet even in the summer or in hotter climates, vitamin D status may be inadequate because of excessive use of sunscreen (which blocks the necessary UV-B radiation) or covering up exposed skin, or because of darker skin pigmentation [92].

Both vitamin D deficiency and insufficiency are of growing concern because they are becoming more common in developed countries. It has been estimated that between 20-80% of US, Canadian, and European adults are vitamin D deficient [92], and affects people of all ages and populations [93,94]. There are well-known and much documented clinical consequences of hypovitaminotic D, including muscle weakness, rickets and osteomalacia [92,95], and an increased intake of vitamin D may be necessary to compensate for these potential complications. Vitamin D also has a vital role in innate and adaptive immunity, and most cells of the immune system express vitamin D receptors [96]. A reduction in vitamin D levels can increase the risk of respiratory infections such as influenza and pneumonia across all age groups [97]. The results from several trials suggest that supplementation with vitamin D can reduce the risk of upper respiratory tract infections and influenza [97].

Insufficient vitamin D levels also have a role in mood disorders such as seasonal affective disorder (SAD) [98,99]. SAD is a type of recurring depression with a seasonal pattern; feelings of low mood, irritability, lethargy and an increased amount of time spent sleeping begins and ends during a specific season (usually winter) every year, with full remittance during other seasons [99]. As many as 15-20% of the general population experiencing 'winter blues', particularly in women and in those in northern latitudes [99]. Vitamin D in particular is thought to have a role in this mood disorder, based on lower vitamin D levels (which fluctuate seasonally in direct relation to the available sunlight) observed in SAD patients and the fact that vitamin D affects the production of both serotonin and dopamine, which both have a key role in SAD [98]. Vitamin D supplementation may help to improve the symptoms of SAD [98], and taking vitamin D before the winter darkness sets in may help to prevent symptoms of depression [100]. Insufficient vitamin D levels may be associated with depression in general, with increasing risk with decreasing vitamin D levels [101], which can be improved with vitamin D supplementation [102].

It is possible that other vitamins (especially the B vitamins and vitamins C, D, and E) and minerals (e.g., calcium, chromium, iron, magnesium, zinc, and selenium) may also have a role in ameliorating mood disorders such as SAD [103]. Although they have not formally been studied in seasonal-dependent mood disorders, micronutrient supplementation has been shown to have beneficial effects on mood in general [103] and can reduce feelings of stress, depression, anxiety and physical or mental fatigue [58,104-109] and increased energy levels, mood, concentration and mental stamina [110-112]. Thus, considering their effects on mood in general, it may be that using a micronutrient supplement during the winter months could help to combat the 'winter blues'.

Summer: Contrary to the demands of the darkness and cold of the winter months, summer places other types of strains on the human body. One consideration during the summer months is the increased likelihood of sweating, as the body tries to maintain a constant, optimal temperature of around 37°C - particularly if a person is exercising [113]. Although sweat is composed principally of water, it also contains electrolytes (sodium, chloride, potassium, magnesium, calcium, phosphate, zinc, iron) that cannot be synthesized in the body and need to be replaced via the diet [113,114]. Sweating, whether heat- or exercise-induced (or both), is associated with a reduced level of several micronutrients (e.g., B vitamins, vitamin C, potassium, calcium, magnesium, iron, zinc) [7,48,115-118]. The number of certain micronutrients lost during sweating can be substantial (Table 3) [118], and intake may need to be increased when living and working in a hot environment to ensure that the RDA is met and homeostasis is restored.

Although there does not seem to be an increased requirement for B vitamins above the RDA in such environments, a deficiency could occur if profuse sweating is combined with suboptimal dietary intake [118]. Long-term exposure to a hot environment, especially in those who are not acclimatized, can compromise vitamin C status and supplementation may be useful in such cases [118]. Exposure to hot temperatures can amplify the increased rate of mineral loss that occurs in sweat with exercise, and marked changes in the metabolism of certain minerals (chromium, copper, iron, magnesium, zinc) have been observed after prolonged, strenuous exercise [118]. It is unclear whether mineral losses resulting from chronic heat exposure or exercise, or both, result in compromised health and performance (endurance capacity, immune defines, antioxidant response, or recovery from illness or trauma) [118].

Micronutrient	Estimated daily loss in sweat, mg
Vitamin B1 (thiamine)	0-1.5*
Vitamin B2 (riboflavin)	0.05-1.2*
Vitamin B3 (nicotinic acid, total)	0.8-1.4*
Vitamin B 5 (pantothenic acid)	0.4-3.0*
B6 (pyridoxine)	0.7*
Folic acid (plus metabolites)	0.026*
Vitamin C	0-5.0*
Iron	1.0-3.0 (men)*
	4.0 (women)*
Iodine	0.146
Magnesium	30-40*
Zinc	5.0-10*
Copper	0-1.0

Table 3: Daily micronutrient loss during sweating in a hot environment [118]. * Based on the fact that working in a hot environment can produce sweat losses of up to 10 liters per day.

Nevertheless, as more sweat is lost the body can become dehydrated and the loss of vital electrolytes can lead to symptoms of tiredness and fatigue, as well as weakness and muscle cramps [119]. Although drinking water can ameliorate these symptoms, water alone is not enough to restore the concentration and composition of the lost electrolytes and cannot replenish micronutrients. Instead, it is important to increase micronutrient intake in situations where there is an increased likelihood of micronutrient loss through intense sweating. Although the increased nutritional demands after sweating are normally met by professional athletes, for example (whose diets are strictly controlled) [120], this may not be true after moderate physical exercise or in the general population when the weather becomes warmer. Eating appears to be a major contributor to maintaining body heat, and if normal food intake continues under conditions of heat stress, the additional heat that must be dissipated may lead to a breakdown in the body's heat mechanisms [118]. Thus, a reduction in

food intake, which is often observed in hotter climates, may actually be a mechanism to cope with hot conditions [118]. Ultimately, the combination of increased micronutrient losses due to intense sweating and a decreased micronutrient intake due to lower overall food intake in hot conditions may lead to an increased risk of micronutrient inadequacies [118].

In people working hard or exercising during the summer months or in hot conditions, supplementation may be required to replenish the electrolytes and micronutrients that may be lost via sweating (e.g., sodium, chloride, potassium, the B vitamins, vitamin C, iron, iodine, magnesium, zinc, copper), particularly if dietary intake decreases, to help restore micronutrient status to homeostatic levels. There may also be a role for antioxidant vitamins (A, C, and E) in reducing lipid peroxidation induced by exercise in a hot environment [118].

Additional demands during the female reproductive cycle: Besides regular seasonal changes placing demands on the body's homeostatic mechanisms to resist various stressors, females of reproductive age are also confronted with regular cyclical changes due to endocrine control of the female reproductive system. This cycle, commonly referred to as the menstrual cycle, is characterized by fluctuations in various hormones that have a broad influence on overall wellbeing, mood, energy levels, and ultimately micronutrient needs. Most women will recognize the feelings of tiredness and fatigue that can occur during menstruation. These are commonly linked to a low iron status [121,122]. It is relatively difficult to remove iron from the body pool once it has entered the body, apart from bleeding - which naturally occurs in women during their period every month [121]. All menstruating women carry an increased risk for iron deficiency due to monthly blood loss [123]. Iron status varies throughout the menstrual cycle [124], but around 10-40 mg of iron is lost in the blood every month [121] and serum ferritin levels are inversely correlated with the duration of menstrual bleeding [125]. Although the prevalence of iron-deficient anaemia has slightly decreased in menstruating women over the years, aided by the use of iron-fortified foods and oral contraceptives (which reduces monthly blood loss) for example, iron deficiency still persists in this population [126]. This may in part be due to significantly lower energy and nutrient intakes that are observed [127]. Inadequate iron intakes are also more likely in female athletes and strict vegetarians [123,128]. Iron supplementation may be necessary in many cases, particularly if menstruation is heavy or prolonged [125]. Iron, of course, is also essential for blood formation, with an essential role in the formation of red blood cells (haematopoiesis) and haemoglobin; about 70% of iron in the body is bound to hemoglobin and facilitates transport of oxygen from the lungs to the rest of the body [129]. An adequate intake of vitamin C is also necessary, as ascorbic acid is known to enhance iron absorption [130]. The metabolism of copper is intertwined with that of iron, and copper deficiency generates cellular iron deficiency [131]. Several other micronutrients have roles in restoring the blood and tissue loss experienced during menstruation. Folate is essential for metabolic pathways involving cell growth, replication and the survival of cells in culture and contributes to normal blood formation [132]. Vitamins B6 and B12 also contribute to the formation of red blood cells: vitamin B12 is required for normal erythrocyte production [133,134], while vitamin B6 also contributes to heme biosynthesis [132]. Vitamin D contributes to normal cell division, and influences the action of many genes that regulate the proliferation, differentiation and apoptosis of cells [135]. Magnesium serves as a regulator of many physiological functions including the maintenance of cellular membrane stability [37], while zinc is also required for normal cell division [136]. Cumulatively all these micronutrients influence red blood cell formation and are therefore critical at times of increased blood losses, as is the case during menstruation.

Menstruation can also induce symptoms of premenstrual syndrome (PMS). Over 150 symptoms have been associated with PMS, but irritability, depression, and fatigue are the most important and most frequently reported affective symptoms [137]. Between 8-20% of women are thought to be affected by PMS [138,139], which is associated with a high and probably underestimated socioeconomic burden [140,141]. Although the causes of PMS are not fully understood, it is likely that micronutrients play a role. For example, calcium intake may contribute to symptoms associated with PMS, and PMS shares some of the same symptoms as hypocalcaemia, including fatigue, depression, anxiety and muscle cramps [142]. A higher intake of both calcium [143-145] and vitamin D (which is necessary for calcium absorption, and which is often deficient in many women) [146,147] has been associated with a lower risk of PMS symptoms. There is also substantial evidence for a role of B vitamins in the pathophysiology of PMS, although the mechanisms are not fully understood. Proposed theories for the pathophysiology of PMS include an interaction of ovarian hormones with neurotransmitters such as serotonin and gamma-amino butyric acid (GABA) and other endocrine systems [148-150]. It is thought that thiamine, riboflavin, niacin, vitamin B6, folate, and vitamin B12 are potentially involved in the numerous metabolic pathways of GABA and serotonin [151,152], and their deficiency may play a role in the development of PMS. Supplementing with vitamin B6 has been shown to alleviate PMS symptoms [153-155], but studies of other vitamins of the B complex are restricted to those that contain a wide variety of micronutrients and the individual effects of each vitamin cannot be isolated [156-158]. During micronutrient supplementation, the menstrual cycle becomes more regular indicating that one of the factors contributing to irregular cycles might be subclinical micronutrient insufficiencies [159]. Low levels of magnesium [160] and zinc [161] have been reported in affective disorders such as PMS which, along with vitamins D and E and manganese, may also play a role in the symptoms of PMS, in reducing blood loss during menstruation, and the severity and duration of menstrual pain [162-165]. An increased intake of minerals and vitamins has been recommended for prevention and treatment of PMS [166,167].

Use of oral contraceptives can reduce blood and tissue loss and symptoms of PMS during menstruation. However, it should be noted that oral contraceptives can have adverse effects on the plasma levels of several micronutrients, including vitamins E and B12, folate, beta-carotene and coenzyme Q10 [168-170]. Therefore, for women on oral contraceptives regular supplementation with multiple vitamins and minerals may help to restore micronutrient levels and aid homeostasis.

Summary

Clearly, micronutrients have a fundamental role in numerous physiological functions, many of which help to regulate the internal environment and enable the body to respond to stressors that may challenge homeostasis. For example, B vitamins are involved in energy production and metabolism, along with vitamin C, iron and several other essential micronutrients. Increased energy expenditure during strenuous activities can lead to a shortage of B vitamins, vitamin C, calcium, iron, zinc, and magnesium, and a suboptimal micronutrient status may affect recovery from such activities. Supplementing with micronutrients during these times can help to boost energy production

and increase energy levels. When we become ill, the absorption and transport of micronutrients may become impaired, metabolic requirements may be increased, and direct micronutrient losses can occur. Given the established importance of micronutrients in immune function, it is likely that suboptimal levels during infection will have an impact on recovery. Supplementation with vitamin C or zinc has been shown to reduce the duration and/or severity of common colds, but few other studies have evaluated the effects of supplementation with other micronutrients. Nevertheless, there is a good rational for ensuring that micronutrient levels are at least optimal to aid recovery during an infection. During the winter, vitamin D supplementation may be necessary to ameliorate the clinical consequences of a low vitamin D status, and reduce the risk of respiratory infections, for example, or season-dependent mood disorders such as SAD. Again, there is a rationale for ensuring adequate levels of micronutrients other than vitamin D, particularly the B vitamins, which may have a beneficial effect on mood. In the heat of summer, the body sweats more, particularly during demanding activities, and vital micronutrients and electrolytes are lost (e.g., sodium, chloride, B vitamins, vitamin C, potassium, calcium, magnesium, iron, zinc). Intake may need to be increased when living and working in a hot environment to ensure that homeostasis is restored. During the challenges faced by women every month as part of the reproductive cycle, tiredness and fatigue that are commonly experienced may be caused by a low iron status. Adequate levels of vitamin C, copper, magnesium, zinc and several B vitamins are also essential to maintain homeostasis during this demanding time. Furthermore, suboptimal levels of calcium, manganese, vitamins D and E, and certain B vitamins may play a role in the development of PMS symptoms. Micronutrient supplementation may be necessary in many women to aid in the restoration of homeostasis and to help combat tiredness, fatigue and PMS.

Therefore, when the body is under additional stress from any external factors that can adversely impact homeostasis, micronutrient supplementation may facilitate numerous physiological processes that occur in response to the homeostatic challenges, helping to restore the internal environment and aid recovery.

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References

1. van den Broek TJ, Kremer BH, Rezende MM, Hoevenaars FP, Weber P, et al. (2017) The impact of micronutrient status on health: correlation network analysis to understand the role of micronutrients in metabolic-inflammatory processes regulating homeostasis and phenotypic flexibility. Genes and Nutri 12: 5.
2. van Ommen B, Fairweather-Tait S, Freidig A, Kardinaal A, Scalbert A, et al. (2008) A network biology model of micronutrient related health. British J Nutrit 99: 72-80.
3. Evans P, Halliwell B (2001) Micronutrients: oxidant/antioxidant status. British J Nutrit 85: 67-74.
4. Haryanto B, Suksmasari T, Wintergerst E, Maggini S (2015) Multivitamin supplementation supports immune function and ameliorates conditions triggered by reduced air quality. Vitam Miner 4: 1318-2376.
5. Morine MJ, Monteiro JP, Wise C, Teitel C, Pence L, et al. (2014) Genetic associations with micronutrient levels identified in immune and gastrointestinal networks. Genes and Nutrit 9: 408.
6. Depeint F, Bruce WR, Shangari N, Mehta R, O'Brien PJ (2006) Mitochondrial function and toxicity: Role of the B vitamin family on mitochondrial energy metabolism. Chemico-Biologi Interact 163: 94-112.
7. Huskisson E, Maggini S, Ruf M (2007) The role of vitamins and minerals in energy metabolism and well-being. J Internat Med Res 35: 277-289.
8. Ommen B, Greef J, Ordovas JM, Daniel H (2014) Phenotypic flexibility as key factor in the human nutrition and health relationship. Genes and Nutrit 9: 423.
9. Schaafsma A, Vries PD, Saris WHM (2001) Delay of natural bone loss by higher intakes of specific minerals and vitamins. Crit Rev Food Sci Nutr 41: 225-249.
10. Arnold M, Barbul A (2006) Nutrition and wound healing. Plast Reconstr Surg 117: 42S-58S.
11. Maggini S, Wintergerst E, Beveridge S, Hornig DH (2007) Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. Br J Nutr 98: S29-S35.
12. Wintergerst ES, Maggini S, Hornig D (2008) Contribution of selected vitamins and trace elements to immune function. Ann Nutr Metab 51: 301-323.
13. Maggini S, Beveridge S, Sorbara J, Senatore G (2008) Feeding the immune system: The role of micronutrients in restoring resistance to infections. 3: 1-21.
14. Roe D (1992) Effects of drugs on vitamin needs. Ann N Y Acad Sci 669: 156-163.
15. Fairfield KM, Fletcher RH (2002) Vitamins for chronic disease prevention in adults: scientific review. JAMA 287: 3116-3126.
16. Fletcher R, Fairfield K (2002) Vitamins for chronic disease prevention in adults. JAMA 287: 3127-3129.
17. Combs JF (2012) The vitamins: Fundamental aspects in Nutrition and Health. Academic Press, London, pp: 1-618.
18. Tortura GJ, Derrickson B (2014) Metabolism and nutrition. Principles of anatomy and physiology, pp: 1-1232.
19. National Institutes of Health (2017) Office of Dietary Supplements. Nutrient recommendations: dietary reference intakes (DRI).
20. D-A-CH (2000) German Nutrition Society (DGE), Austrian Nutrition Society (OGE), Swiss Society for Nutrition Research (SGE) and Swiss Nutrition Association (SVE). Reference values for nutrient intake.
21. Australian Government Ministry of Health, Department of Health and Ageing and National Health and Medical Research Council (2005) Nutrient reference values for Australia and New Zealand including recommended dietary intakes.
22. Japan Ministry of Health Labour and Welfare (2015) Overview of dietary reference intakes for Japanese.
23. UK Government and Department for Environment Food & Rural Affairs (2014) Reference nutrient intakes. Guidance: Family Food Methodology.
24. Elmadfa I, Meyer A, Nowak V, Hasenegger V, Putz P, et al. (2009) European Nutrition and Health Report. Forum Nutr 62: 1-405.
25. Troesch B, Hoeft B, McBurney M, Eggersdorfer M, Weber P (2012) Dietary surveys indicate vitamin intakes below recommendations are common in representative Western countries. Br J Nutr 108: 692-698.
26. Mensink G, Fletcher R, Gurinovic M, Huybrechts I, Lafay L, et al. (2013) Mapping low intake of micronutrients across Europe. Br J Nutr 110: 755-773.
27. Huskisson E, Maggini S, Ruf M (2007) The influence of micronutrients on cognitive function and performance. J Int Med Res 35: 1-19.
28. Kennedy DO, Stevenson EJ, Jackson PA, Dunn S, Wishart K, et al. (2016) Multivitamins and minerals modulate whole-body energy metabolism and cerebral blood-flow during cognitive task performance: a double-blind, randomised, placebo-controlled trial. Nutr Metab 13: 51-60.
29. Depeint F, Bruce WR, Shangari N, Mehta R, O'Brien PJ (2006) Mitochondrial function and toxicity: Role of the B vitamin family on the one-carbon transfer pathways. Chem Biol Interact 163: 113-132.

30. Ricci JA, Chee E, Lorandeau AL, Berger J (2007) Fatigue in the US workforce: prevalence and implications for lost productive work time. J Occup Environ Med 49: 1-10.
31. Wilson J, Morgan S, Magin PJ, van Driel ML (2014) Fatigue-A rational approach to investigation. Aust Fam Physician 43: 457-461.
32. British Medical Journal (2016) Assessment of fatigue.
33. Driskell JA, Wolinsky I (1999) Energy-yielding macronutrients and energy metabolism in sports nutrition, CRC Press.
34. Driskell JA, Wolinsky I (1999) Macroelements, water, and electrolytes in sports nutrition. CRC Press.
35. Armstrong LE, Maresh CM (1996) Vitamin and mineral supplements as nutritional aids to exercise performance and health. Nutr Rev 54: S149-S158.
36. Belko AZ, Obarzanek E, Kalkwarf HJ, Rotter MA, Bogusz S, et al. (1983) Effects of exercise on riboflavin requirements of young women. Am J Clin Nutr 37: 509-517.
37. Lukaski H, Nielsen F (2002) Dietary magnesium depletion affects metabolic responses during submaximal exercise in postmenopausal women. J Nutr 132: 930-935.
38. Córdova A, Navas FJ (1998) Effect of training on zinc metabolism: changes in serum and sweat zinc concentrations in sportsmen. Ann Nutr Metab 42: 274-282.
39. http://www.tandfonline.com/doi/abs/10.1080/0264041031000140563
40. Woolf K, Manore MM (2006) B-vitamins and exercise: does exercise alter requirements. Int J Sport Nutr Exerc Metab 16: 453-484.
41. Rokitzki L, Sagredos A, Reuss F, Petersen G, Keul J (1993) Pantothenic acid levels in blood of athletes at rest and after aerobic exercise. Z Ernahrungswiss 32: 282-288.
42. IOM (Institute of Medicine) (1998) Reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. National Academy Press, Washington DC.
43. van der Beek E, van Dokkum W, Schrijver J, Wedel M, Gaillard A, et al. (1988) Thiamin, riboflavin, and vitamins B-6 and C: impact of combined restricted intake on functional performance in man. Am J Clin Nutr 48: 1451-1462.
44. Johnston C, Swan P, Corte C (1999) Substrate utilization and work efficiency during submaximal exercise in vitamin C depleted-repleted adults. Int J Vitam Nutr Res 69: 41-44.
45. Rodriguez N, Di Marco N, Langley S (2009) American College of Sports Medicine position stand. Nutrition and athletic performance. Med Sci Sports Exerc 41: 709-731.
46. Laires M, Monteiro C (2008) Exercise, magnesium and immune function. Magnes Res 21: 92-96.
47. Nielsen F, Lukaski H (2006) Update on the relationship between magnesium and exercise. Magnes Res 19: 180-189.
48. McDonald R, Keen C (1988) Iron, zinc and magnesium nutrition and athletic performance. Sports Med 5: 171-184.
49. Sandström B (1991) Zinc: the functional significance of marginal deficiency. Modern lifestyles, lower energy intake and micronutrient status. Pietrzik K (ed.), Springer Verlag, London, pp: 1-19.
50. Lukaski H (2004) Vitamin and mineral status: effects on physical performance. Nutrition 20: 632-644.
51. Ganapathy S, Volpe S (1999) Zinc, exercise, and thyroid hormone function. Crit Rev Food Sci Nutr 39: 369-390.
52. Lukaski H (2005) Low dietary zinc decreases erythrocyte carbonic anhydrase activities and impairs cardiorespiratory function in men during exercise. Am J Clin Nutr 81: 1045-1051.
53. Smidt LJ, Cremin FM, Grivetti LE, Clifford AJ (1991) Influence of thiamin supplementation on the health and general well-being of an elderly irish population with marginal thiamin deficiency. J Gerontol 46: 16-22.
54. Benton D, Griffiths R, Haller J (1997) Thiamine supplementation mood and cognitive functioning. Psychopharmacol 129: 66-71.
55. Verdon F, Burnand B, Stubi C, Bonard C, Graff M, et al. (2003) Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. BMJ 326: 1124.
56. Joint World Health Organization/Centers for Disease Control and Prevention Technical Consultation on the Assessment of Iron Status at the Population Level (2007) Assessing the iron status of populations: including literature reviews: report of a Joint World Health Organization/ Centers for Disease Control and Prevention Technical Consultation on the Assessment of Iron Status at the Population Level, Geneva, Switzerland, 6–8 April 2004. Second, World Health Organization, Geneva, Switzerland.
57. Popovic IC (1993) Neurotrope Vitamin-Mineralstoff-Kombination in der Stress-Therapie. Schweiz Zeitschr Ganzh Med 3: 140-143.
58. Haskell CF, Robertson B, Jones E, Forster J, Jones R, et al. (2010) Effects of a multi-vitamin/mineral supplement on cognitive function and fatigue during extended multi-tasking. Hum Psychopharmacol 25: 448-461.
59. Nowak A, Boesch L, Andres E, Battegay E, Hornemann T, et al. (2016) Effect of vitamin D3 on self-perceived fatigue: A double-blind randomized placebo-controlled trial. Medicine 95: 52-53.
60. Dominguez L, Barbagallo M, Lauretani F, Bandinelli S, Bos A, et al. (2006) Magnesium and muscle performance in older persons: the InCHIANTI study. Am J Clin Nutr 84: 419-426.
61. Volpe S (2015) Magnesium and the Athlete. Curr Sports Med Rep 14: 279-283.
62. Brilla L, Haley T (1992) Effect of magnesium supplementation on strength training in humans. J Am Coll Nutr 11: 326-329.
63. Krotkiewski M, Gudmundsson M, Backstrom P, Mandroukas K (1982) Zinc and muscle strength and endurance. Acta Physiol Scand 116: 309-311.
64. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, et al. (1994) The chronic fatigue syndrome: A comprehensive approach to its definition and study. Ann Intern Med 121: 953-959.
65. Maric D, Brkic S, Mikic AN, Tomic S, Cebovic T, et al. (2014) Multivitamin mineral supplementation in patients with chronic fatigue syndrome. Med Sci Monit 20: 47-53.
66. Werbach M (2000) Nutritional strategies for treating chronic fatigue syndrome. Altern Med Rev 5: 93-108.
67. Parkin J, Cohen B (2001) An overview of the immune system. Lancet 357: 1777-1789.
68. Beck M (2000) Nutritionally induced oxidative stress: effect on viral disease. Am J Clin Nutr 71: 1676-1681.
69. Katona P, Katona-Apte J (2008) The interaction between nutrition and infection. Clin Infect Dis 46: 1582-1588.
70. Stephensen CB (1999) Burden of infection on growth failure. J Nutr 129: 534-538.
71. Jackson A, Calder P (2004) Severe undernutrition and immunity. Handbook of Nutrition and Immunity, Springer Science & Business Media, Berlin, Germany.
72. Ramakrishnan U, Webb AL, Ologoudou K (2004) Infection, immunity, and vitamins. Handbook of Nutrition and Immunity. Springer Science & Business Media, Berlin, Germany.
73. Gruys E, Toussaint M, Niewold T, Koopmans S (2005) Acute phase reaction and acute phase proteins. J Zhejiang Univ Sci B 6: 1045-1056.
74. Hemilä H, Chalker E (2013) Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 1: CD000980.
75. Hemilä H (2017) Vitamin C and infections. Nutrients 9: 339.
76. Hemilä H, Petrus EJ, Fitzgerald JT, Prasad A (2016) Zinc acetate lozenges for treating the common cold: an individual patient data meta-analysis. Br J Clin Pharmacol 82: 1393-1398.
77. Hemilä H (2011) Zinc lozenges may shorten the duration of colds: a systematic review. Open Respir Med J 5: 51-58.
78. Hemilä H, Fitzgerald JT, Petrus EJ, Prasad A (2017) Zinc acetate lozenges may improve the recovery rate of common cold patients: An individual patient data meta-analysis. Open Forum Infect Dis 4: ofx059.

79. Meydani SN, Han SN, Hamer DH (2004) Vitamin E and respiratory infection in the elderly. Ann N Y Acad Sci 1031: 214-222.
80. Tamura J, Kubota K, Murakami H, Sawamura M, Matsushima T, et al. (1999) Immunomodulation by vitamin B12: augmentation of CD8+ T lymphocytes and natural killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. Clin Exp Immunols 116: 28-32.
81. Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, et al. (2006) Epidemic influenza and vitamin D. Epidemiology & Infection 134: 1129-1140.
82. Langdon A, Crook N, Dantas G (2016) The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. Genome Medicine 8: 39.
83. Lange K, Buerger M, Stallmach A, Bruns T (2016) Effects of antibiotics on gut microbiota. Digestive Diseases 34: 260-268.
84. Jungersen M, Wind A, Johansen E, Christensen JE, Stuer-Lauridsen B, et al. (2014) The Science behind the Probiotic Strain Bifidobacterium animalis subsp. lactis BB-12®. Microorganisms 2: 92-110.
85. Jones K (2010) Probiotics: Preventing Antibiotic-Associated Diarrhea. Journal for Specialists in Pediatric Nursing 15: 160-162.
86. Roe DA (1989) Drug-nutrient interactions in the elderly. Nutrition, Aging and the Elderly.
87. Roe D (1993) Drug-nutrient interactions. Human Nutrition and Dietetics. Garrow J, James W, Ralph A (eds.), Churchill Livingstone, Edinburgh Ch, New York, pp: 1-856.
88. Karadima V, Kraniotou C, Bellos G, Tsangaris GT (2016) Drug-micronutrient interactions: food for thought and thought for action. EPMA Journal 7: 10.
89. O'Dell BL (1989) Mineral interactions relevant to nutrient requirements. The Journal of Nutrition 119: 1832-1838.
90. Institute of Medicine (IOM) (1997) Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. National Acdemy Press, Washington, DC.
91. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (1997) Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academies Press (US).
92. Hossein-nezhad A, Holick MF (2013) Vitamin D for health: a global perspective. In Mayo Clinic Proceedings, Elsevier 88: 720-755.
93. Holick MF (2006) High prevalence of vitamin D inadequacy and implications for health. In Mayo Clinic Proceedings, Elsevier 81: 353-373.
94. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, et al. (2012) Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. The Journal of Clinical Endocrinology & Metabolism 97: 1153-1158.
95. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, et al. (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism 96: 1911-1930.
96. Veldman CM, Cantorna MT, DeLuca HF (2000) Expression of 1, 25-dihydroxyvitamin D3 receptor in the immune system. Archives of Biochemistry and Biophysics 374: 334-338.
97. Watson RR (2015) Foods and Dietary Supplements in the Prevention and Treatment of Disease in Older Adults. Academic Press.
98. Stewart AE, Roecklein KA, Tanner S, Kimlin MG (2014) Possible contributions of skin pigmentation and vitamin D in a polyfactorial model of seasonal affective disorder. Medical Hypotheses 83: 517-525.
99. Melrose S (2015) Seasonal affective disorder: an overview of assessment and treatment approaches. Depression Research and Treatment.
100. Kerr DC, Zava DT, Piper WT, Saturn SR, Frei B, et al. (2015) Associations between vitamin D levels and depressive symptoms in healthy young adult women. Psychiatry Research 227: 46-51.
101. Anglin RE, Samaan Z, Walter SD, McDonald SD (2013) Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Br J Psych 202: 100-107.
102. Shaffer JA, Edmondson D, Wasson LT, Falzon L, Homma K, et al. (2014) Vitamin D supplementation for depressive symptoms: A systematic review and meta-analysis of randomized controlled trials. Psychosom Med 76: 190-196.
103. Kaplan BJ, Crawford SG, Field CJ, Simpson JS (2007) Vitamins, minerals, and mood. Psychol Bul 133: 747-760.
104. Kennedy D, Veasey R, Watson A, Dodd F, Jones E, et al. (2010) Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males. Psychopharmacology (Berl) 211: 55-68.
105. Harris E, Kirk J, Rowsell R, Vitetta L, Sali A, et al. (2011) The effect of multivitamin supplementation on mood and stress in healthy older men. Hum Psychopharmacol 26: 560-567.
106. Pipingas A, Camfield D, Stough C, Cox K, Fogg E, et al. (2013) The effects of multivitamin supplementation on mood and general well-being in healthy young adults. A laboratory and at-home mobile phone assessment. Appetite 69: 123-136.
107. Stough C, Scholey A, Lloyd J, Spong J, Myers S, et al. (2011) The effect of 90 day administration of a high dose vitamin B-complex on work stress. Hum Psychopharmacol 26: 470-476.
108. White DJ, Cox KH, Peters R, Pipingas A, Scholey AB (2015) Effects of four-week supplementation with a multi-vitamin/mineral preparation on mood and blood biomarkers in young adults: A randomised, double-blind, placebo-controlled trial. Nutrients 7: 9005-9017.
109. Macpherson H, Rowsell R, Cox KH, Reddan J, Meyer D, et al. (2016) The effects of four-week multivitamin supplementation on mood in healthy older women: A randomized controlled trial. Evid Based Complement Alternat Med 2016: 1-11.
110. Sarris J, Moylan S, Camfield DA, Pase MP, Mischoulon D, et al. (2012) Complementary medicine, exercise, meditation, diet, and lifestyle modification for anxiety disorders: a review of current evidence. Evid Based Complement Alternat Med.
111. Kennedy DO, Veasey RC, Watson AW, Dodd FL, Jones EK, et al. (2011) Vitamins and psychological functioning: a mobile phone assessment of the effects of a B vitamin complex, vitamin C and minerals on cognitive performance and subjective mood and energy. Hum Psychopharmacol 26: 338-347.
112. Jaatinen N, Korpela R, Poussa T, Turpeinen A, Mustonen S, et al. (2014) Effects of daily intake of yoghurt enriched with bioactive components on chronic stress responses: a double-blinded randomized controlled trial. Int J Food Sci Nutr 65: 507-514.
113. Institute of Medicine (IOM); Panel on Micronutrients, SCotSEoDRI (2000) Dietary reference intakes for vitamin C, vitamin E, selenium and carotenoids. National Academy Press, Washington DC.
114. Hosey RG, Glazer JL (2004) The ergogenics of fluid and electrolyte balance. Curr Sports Med Rep 3: 219-223.
115. Tang YM, Wang DG, Li J, Li XH, Wang Q, et al. (2016) Relationships between micronutrient losses in sweat and blood pressure among heat-exposed steelworkers. Ind Health 54: 215-223.
116. Fogelholm M (1999) Micronutrients: interaction between physical activity, intakes and requirements. Public Health Nutr 2: 349-356.
117. Anderson RA, Polanski MM, Bryden NA (1984) Strenuous running: acute effects on chromium, copper, zinc and selected clinical variables in urine and serum of male runners. Biol Trace Elem Res 6: 327-336.
118. Marriott B (1993) Nutritional needs in hot environments: applications for military personnel in field operations.
119. Tortura GJ, Derrickson B (2014) Fluid, electrolyte, and acid-base homeostasis. Principles of anatomy and physiology. John Wiley & Sons, pp: 1- 27.
120. Zimmermann MB (2003) Vitamin and mineral supplementation and exercise performance. Schweizerische Zeitschrift fur Sportmedizin und Sporttraumatologie 51: 53-57.
121. Angeli A, Lainé F, Lavenu A, Ropert M, Lacut K, et al. (2016) Joint model of iron and hepcidin during the menstrual cycle in healthy women. AAPS J 18: 490-504.

122. Tortura GJ, Derrickson B (2014) The cardiovascular system: the blood. Principles of anatomy and physiology. pp: 1-19.
123. Akabas S, Dolins K (2005) Micronutrient requirements of physically active women: what can we learn from iron? Am J Clin Nutr 81: 1246-1251.
124. Kim I, Yetley EA, Calvo MS (1993) Variations in iron-status measures during the menstrual cycle. Am J Clin Nutr 58: 705-709.
125. Milman N, Clausen J, Byg KE (1998) Iron status in 268 Danish women aged 18-30 years: influence of menstruation, contraceptive method, and iron supplementation. Ann Hematol 77: 13-19.
126. Hercberg S, Preziosi P, Galan P (2001) Iron deficiency in Europe. Public Health Nutr 4: 537-545.
127. Cheikh Ismail LI, Al-Hourani H, Lightowler HJ, Aldhaheri AS, Henry CJ (2009) Energy and nutrient intakes during different phases of the menstrual cycle in females in the United Arab Emirates. Ann Nutr Metab 54: 124-128.
128. McClung JP, Gaffney-Stomberg E, Lee J (2014) Female athletes: A population at risk of vitamin and mineral deficiencies affecting health and performance. J Trace Elem Med Biol 28: 388-392.
129. Gupta C (2014) Role of iron (Fe) in body. IOSR-JAC 7: 38-46.
130. Atanassova BD, Tzatchev KN (2008) Ascorbic acid--important for iron metabolism. Folia Med (Plovdiv) 50: 11-16.
131. Arredondo M, Nunez M (2005) Iron and copper metabolism. Mol Aspects Med 26: 313-327.
132. Stargrove M, Treasure J, McKee D (2008) Herb, nutrient, and drug interactions: Clinical implications and therapeutic strategies, St. Louis, Missouri, pp: 1-960.
133. Koury MJ, Ponka P (2004) New insights into erythropoiesis: the roles of folate, vitamin B12, and iron. Annu Rev Nutr 24: 105-131.
134. IOM (1998) Dietary reference intakes for thiamine, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Thiamine. Washington D. C: National Academy Press, pp: 58-86.
135. IOM (Institute of Medicine) (2011) Dietary reference intakes for calcium and vitamin D.
136. MacDonald RS (2000) The role of zinc in growth and cell proliferation. J Nutr 130: 1500-1508.
137. Mortola JF (1992) Issues in the diagnosis and research of premenstrual syndrome. Clin Obstet Gynecol 35: 587-598.
138. American College of Obstetrics and Gynaecology (2000) Premenstrual syndrome. ACOG Pract Bull 15: 206-218.
139. Deuster PA, Adera T, South-Paul J (1999) Biological, social, and behavioral factors associated with premenstrual syndrome. Arch Fam Med 8: 122-128.
140. Borenstein J, Chiou CF, Dean B, Wong J, Wade S (2005) Estimating direct and indirect costs of premenstrual syndrome. J Occup Environ Med 47: 26-33.
141. Mishell DR (2005) Premenstrual disorders: epidemiology and disease burden. Am J Manage Care 11: 476-479.
142. Thys-Jacobs S (2000) Micronutrients and the premenstrual syndrome: the case for calcium. J Am Coll Nutr 19: 220-227.
143. Thys-Jacobs S, Starkey P, Bernstein D, Tian J (1998) Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual Syndrome Study Group. Am J Obstet Gynecol 179: 444-452.
144. Ghanbari Z, Haghollahi F, Shariat M, Foroshani AR, Ashrafi M (2009) Effects of calcium supplement therapy in women with premenstrual syndrome. Taiwan J Obstet Gynecol 48: 124-129.
145. Penland JG, Johnson PE (1993) Dietary calcium and manganese effects on menstrual cycle symptoms. Am J Obstet Gynecol 168: 1417-1423.
146. Schaefer E (2016) Micronutrient deficiency in women living in industrialized countries during the reproductive years: Is there a basis for supplementation with multiple micronutrients? J Nutr Disorders Ther 6: 1-8.
147. Bertone-Johnson ER, Hankinson SE, Bendich A, Johnson SR, Willett WC, et al. (2005) Calcium and vitamin D intake and risk of incident premenstrual syndrome. Arch Intern Med 165: 1246-1252.
148. Halbreich U (2003) The etiology, biology, and evolving pathology of premenstrual syndromes. Psych Neuroendocrinology 28: 55-99.
149. Backstrom T, Andreen L, Birzniece V, Björn I, Johansson IM, et al. (2003) The role of hormones and hormonal treatments in premenstrual syndrome. CNS Drugs 17: 325-342.
150. Mortola J (1998) Premenstrual syndrome--pathophysiologic considerations. New Eng J Med 338: 256-257.
151. Bourre JM (2006) Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 1: micronutrients. J Nutr Health Aging 10: 377-385.
152. Stipanuk MH (2006) Biochemical, physiological, & molecular aspects of human nutrition. Saunders Elsevier, St. Louis, pp: 1-90
153. Kashanian M, Mazinani R, Jalalmanesh S (2007) Pyridoxine (vitamin B6) therapy for premenstrual syndrome. Int J Gynaecol Obstet 96: 43-44.
154. De Souza MC, Walker AF, Robinson PA, Bolland K (2000) A synergistic effect of a daily supplement for 1 month of 200 mg magnesium plus 50 mg vitamin B6 for the relief of anxiety-related premenstrual symptoms: a randomized, double-blind, crossover study. J Womens Health Gend Based Med 9: 131-139.
155. Wyatt KM, Dimmock PW, Jones PW, Shaughn O'Brien PM (1999) Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. BMJ 318: 1375-1381.
156. London RS, Bradley L, Chiamori NY (1991) Effect of a nutritional supplement on premenstrual symptomatology in women with premenstrual syndrome: a double-blind longitudinal study. J Am Coll Nutr 10: 494-499.
157. Facchinetti F, Nappi RE, Sances MG, Neri I, Grandinetti G, et al. (1997) Effects of a yeast-based dietary supplementation on premenstrual syndrome. A double-blind placebo-controlled study. Gynecol Obstet Invest 43: 124-124.
158. Goei GS, Abraham GE (1983) Effect of a nutritional supplement, optivite, on symptoms of premenstrual tension. J Reprod Med 28: 527-531.
159. Dudas I, Rockenbauer M, Czeizel A (1995) The effect of preconceptional multivitamin supplementation on the menstrual cycle. Arch Gynecol Obstet 256: 115-123.
160. Rosenstein DL, Elin RJ, Hosseini JM, Grover G, Rubinow DR (1994) Magnesium measures across the menstrual cycle in premenstrual syndrome. Biol Psychiatry 35: 557-561.
161. Amani R, Saeidi S, Nazari Z, Nematpour S (2010) Correlation between dietary zinc intakes and its serum levels with depression scales in young female students. Biol Trace Elem Res 137: 150-158.
162. Ziaei S, Faghihzadeh S, Sohrabvand F, Lamyian M, Emamgholy T (2001) A randomised placebo-controlled trial to determine the effect of vitamin E in treatment of primary dysmenorrhoea. BJOG 108: 1181-1183.
163. Ziaei S, Zakeri M, Kazemnejad A (2005) A randomised controlled trial of vitamin E in the treatment of primary dysmenorrhoea. BJOG 112: 466-469.
164. Dennehy C (2006) The use of herbs and dietary supplements in gynecology: an evidence-based review. J Midwifery Womens Health 51: 402-409.
165. Jarvis C, Lynch A, Morin A (2008) Management strategies for premenstrual syndrome/premenstrual dysphoric disorder. Ann Pharmacother 42: 967-978.
166. American College of Obstetrics and Gynecology Practice Bulletin (2000) Clinical management guidelines for obstetricians-gynecologists. Obstet Gynecol 95: 1-9.
167. Bendich A (2000) The potential for dietary supplements to reduce premenstrual syndrome (PMS) symptoms. J Am Coll Nutr 19: 3-12.
168. Palan P, Magneson A, Castillo M, Dunne J, Mikhail M (2006) Effects of menstrual cycle and oral contraceptive use on serum levels of lipid-soluble antioxidants. Am J Obstet Gynecol 194: 35-38.

169. Sutterlin M, Bussen S, Rieger L, Dietl J, Steck T (2003) Serum folate and Vitamin B12 levels in women using modern oral contraceptives (OC) containing 20 microg ethinyl estradiol. Eur J Obstet Gynecol Reprod Biol 107: 57-61.

170. Berg G, Kohlmeier L, Brenner H (1997) Use of oral contraceptives and serum beta-carotene. Eur J Clin Nutr 51: 181-187.

171. Deparment of Health (1991) Report on Health and Social Subjects 41 – Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. Report of the panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy.

172. Linus Pauling Institute and Oregon State University (2017) Micronutrient Information Centre.

173. Wasserman RH (2004) Vitamin D and the dual processes of intestinal calcium absorption. J Nutr 134: 3137-3139.

174. Kennedy DO (2016) B vitamins and the brain: Mechanisms, dose and efficacy—a review. Nutrients 8: 1-68.