NFS Journal 11 (2018) 1–11

Contents lists available at ScienceDirect

NFS Journal

journal homepage: www.elsevier.com/locate/nfs

Review article

Micronutrients in the life cycle: Requirements and sufficient supply

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ARTICLE INFO

Keywords:
Micronutrients
Recommended dietary allowance (RDA)
Life cycle
Sufficient supply
Safety
Deficiency

ABSTRACT

Macronutrients (fat, protein, carbohydrates) deliver energy and important material to ensure the entire body composition. Micronutrients are needed to keep this process of continuous construction and re-construction running. Consequently, the requirement for micronutrients will differ depending on the individual need which is related to the different metabolic conditions within the life cycle. Within the first 1000 days of life, from conception to the end of the second year of life the requirement for micronutrients is high and if the supply is inadequate that might have consequences for physical and at least cognitive development. In particular, iron, iodine, vitamin D and folate are micronutrients which might become critical during that period. Due to the fact that clinical symptoms of deficiencies develop late, but inadequate supply of one or more micronutrients may have consequences for health the term hidden hunger has been introduced to describe that situation. In particular the time period of pregnancy and early childhood is critical and hidden hunger is a worldwide problem, affecting > 2 billion people, primarily females and children. The importance of different requirements during the life cycle is usually not considered. In addition, we do not really know what the individual requirement is. The estimation of the requirement is based on studies calculating the supply of a micronutrient to avoid a deficiency disease within a healthy population and is not based on sound scientific methodology or data. We need to consider that at different moments in the life cycle the supply might become critical in particular in case of a disease or sudden increase of metabolic turnover. In this narrative review we summarize data from studies dealing with different micronutrient requirements in pregnancy, exercise, vegan diet, adolescents and elderly. Knowledge of critical periods and related critical micronutrients might help to avoid hidden hunger and its consequences.

1. Introduction

Humans need energy delivering macronutrients (fat, carbohydrate, protein) and no energy-delivering micronutrients. Regarding energy supply one macronutrient can substitute the other for a restricted time period. A life with either low fat or low carbohydrate or low protein supply is possible. To ensure the metabolic pathways and at least function of macronutrients the micronutrients are indispensable. In contrast to the macronutrients they cannot substitute each other and they cannot be synthesized within the body. Consequently we depend on the delivery of all the essential micronutrients via our diet. Whether the micronutrient supply via our diet fulfills our requirement or not depends on a couple of circumstances such as age, life style, hormonal activity or exercise and at least on bioavailability and half-life of the micronutrient.

In general it is claimed that adequate micronutrient supply can be achieved via a mixed diet. But what is adequate? Due to the fact that the metabolic and functional demand of micronutrients might be different, e.g. during childhood growth, adolescence or pregnancy, the requirement may differ and may lead to inadequacy.

We need to understand

- the definition of requirement
- whether there is any risk if a requirement is not achieved
- whether different age groups may have different requirements
- which micronutrients might be critical
- whether inadequate supply may have consequences in the short or long term

The above cited items seem rather simple. However, our knowledge regarding requirement, risk of inadequate supply and impact on health and adequate development is more or less superficial. The existing data show inadequate supply according to the claimed requirement. There might be a harmful impact in particular during pregnancy and early

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https://doi.org/10.1016/j.nfs.2018.03.001
Received 17 November 2017; Received in revised form 16 March 2018; Accepted 23 March 2018
Available online 27 March 2018
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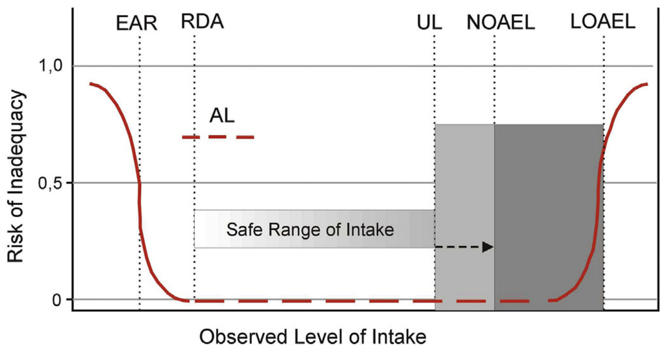

Fig. 1. Definition of different levels of intake: RDA: recommended dietary allowances; AI: acceptable intake (is used if an EAR or RDA could not be calculated); UL: upper level, the amount of a micronutrient below the amount which shows any kind of side effects; NOAEL: pharmacological definition of a no observed adverse effect level, similar to UL; LOAEL: lowest observed adverse effect level, the level which shows side effects.
Source: [1 modfied 3].

childhood but further data regarding long-term health and consequences of not achieving the requirements are needed to estimate the risk of low micronutrient supply. The data analysis below will try to summarize the existing data of micronutrient supply during the life style and some consequences if the intake is low.

2. Dietary reference intakes

The Institute of Medicine (IOM) of the US [1] presented the concept of "Dietary Reference Intakes" (DRI). According to the IOM are quantitative estimates of nutrient intakes to be used for planning and assessing diets for apparently healthy people (Fig. 1).

The following terms are used by IOM:

Recommended dietary allowances (*RDA*): the dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98%) healthy individuals in a particular life stage and gender group.
Adequate intake (*AI*): a recommended intake value based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of healthy people that are assumed to be adequate – used when an RDA cannot be determined.
Tolerable upper intake level (*UL*): the highest level of nutrient intake that is likely to pose no risk of adverse health effects for almost all indviduals in the general population. As intake increases above the UL, the risk of adverse effects increases.
Estimated Average Requirement (*EAR*): a nutrient intake value that is estimated to meet the requirement of half of the healthy individuals in a life stage and gender group.

Very recently the European Food Safety Authority (EFSA) summarized the reports on micronutrient requirements of EFSA scientific panels since 2010 [2].

Instead of RDA the *Population Reference Intake* (PRI) is defined as the level of (nutrient) intake that is adequate for virtually all people in a population group. The term Average requirement (AR) is used instead of EAR and a new term the *Lower Threshold Intake* (LTI) is introduced. The LTI is the level of intake below which, on the basis of current knowledge, almost all people will be unable to maintain "metabolic integrity", according to the criterion chosen for each nutrient.

The differences between the IOM RDA and the EFSA PRI values are not substantial. In some cases the EFSA recommended intakes are slightly lower (e.g. vitamin A, Folate) or slightly higher (vitamin C, vitamin B12). However, because the values are based on either EAR or AR these differences are not really justified.

2.1. Estimated average requirement

To understand the impact of adequate micronutrient supply it is necessary to define the margins of adequate and inadequate and to discuss their impact on health and disease.

This estimation is based on specific indicators which are taken as a criterion of adequacy, e.g. absence of night blindness (vitamin A) or osteomalazia (vitamin D) or anemia (iron) in half of the apparently healthy individuals in a life stage or gender group. In most cases only small studies exist which are the basis for the criteria to calculate the EAR. If an EAR cannot be calculated an acceptable intake (AI) is determined. Consequently an EAR is a population-related value and not an individual one. The aim of the definition of an EAR is to calculate the mean intake based on the diet of a healthy adult population which seems adequate to avoid a micronutrient deficiency in 50% of the population. Individuals on the right side of this Gaussian distribution have a lower risk for a deficiency, those on the left a higher risk (Fig. 1). Thus, the EAR is only useful in populations with similar dietary composition. This explains differences between different populations. Nevertheless in many cases the EAR levels are used without discriminating country and population specific data.

EARs related to either life style, age or gender are extrapolated from the existing EAR for a given micronutrient with regard to the average healthy population without further scientific evaluation.

Based on current data a couple of US citizens (from the age of 1) do not even meet the EAR (Table 1).

Inadequate supply with micronutrients is not only present in low-income countries, it also occurs increasingly in high-income countries, e.g. in the US and Europe [5].

In a recent Europe-wide study, the percentage of healthy people (adults aged 19–64 years) and elderly (aged > 64 years) below the EAR (as defined by IOM [1]) has been reported based on different national surveys (Tables 2a, 2b and 3a, 3b) [6].

The data above show that inadequate micronutrient supply is not only present in low- income countries but also in high-income countries. Depending on the countries the magnitude can differ. This shows that food availability, dietary traditions and behaviors have a strong impact on micronutrient supply. If we consider that the amount of micronutrients which should be supplied (according to RDA) differs with respect to age, gender and life style, the number of people with inadequate supply may even increase.

What does it mean if the population does not reach the EAR for different micronutrients? Supply below EAR increases the risk for a clinical deficiency.

Indeed, based on the definition of the EAR, there might be an increased risk for developing a deficiency disease. This is in particular of importance if the requirement is substantially increased, e.g. in cases of a disease, accelerated growth or pregnancy.

Table 1
Percentage of US citizens not meeting the EAR for selected nutrients.
Source: [4].

Micronutrient	US citizens not meeting the EAR for selected nutrients [%]
Riboflavin	10.9
Niacin	12.7
Thaimin	18.4
Vitamin B12	20.3
Vitamin B6	26.1
Folate	40.3
Vitamin C	49.0
Vitamin A	54.0
Vitamin E	86.4
Zinc	29.2
Magnesium	57.0

Table 2a
Percentage of adults (19–64 years) below the EAR for some vitamins. Abbreviations: m: males; f: females.

Country	Vitamin C [mg/day] (EAR: m: 60 mg/day, f: 50 mg/day)	Vitamin D [µg/day] (EAR: m, f: 10 µg/day)	Folic acid [µg/day] (EAR: m, f: 200 µg/day)	Vitamin B12 [µg/day] (EAR: m, f: 1,4 µg/day)
	m/f	m/f	m/f	m/f
Germany	19/11	96/100	28/27	8/8
Ireland	40/37	100/100	10/20	14/23
Sweden	34/21	93/100	33/41	8/20
United Kingdom	36/34	97/100	18/26	13/10
Denmark	23/17	99/100	15/19	9/13
Finland	22/17	96/100	28/38	21/18

Table 2b
Percentage of elderly (> 64 years) below the EAR for some vitamins. Abbreviations: m: males; f: females.

Country	Vitamin C [mg/day] (EAR: m: 60 mg/day, f: 50 mg/day)	Vitamin D [µg/day] (EAR: m, f: 10 µg/day)	Folic acid [µg/day] (EAR: m, f: 200 µg/day)	Vitamin B12 [µg/day] (EAR: m, f: 1,4 µg/day)
	m/f	m/f	m/f	m/f
Germany	12/11	91/99	21/21	4/7
Denmark	25/17	98/100	19/19	8/10
Finland	33/25	55/78	34/46	20/21

Table 3a
Percentage of adults (19–64 years) below the EAR for minerals and trace elements. Abbreviations: m: males; f: females; n.d.: not determined.

Country	Calcium [mg/day] (EAR: m/f: 800 mg/day)	Zinc [mg/day] (EAR: m: 6.4 mg/day, f: 5.7 mg/day)	Selenium [µg/day] (EAR: m: 35 µg/day, f: 30 µg/day)	Iodine [µg/day] (EAR: m, f: 100 µg/day)
	m/f	m/f	m/f	m/f
Germany	25/26	10/10	n.d.	43/49
Ireland	34/58	12/29	n.d.	n.d.
Sweden	25/34	3/4	47/47	n.d.
United Kingdom	35/61	16/31	n.d.	n.d.
Denmark	28/31	5/6	31/36	6/10
Finland	25/33	7/10	8/10	24/22

Table 3b
Minerals and trace elements (elderly > 64 years) below the EAR for some vitamins. Abbreviations: m: males; f: females; n.d.: not determined.

Country	Calcium [mg/day] (EAR: m/f: 800 mg/day)	Zinc [mg/day] (EAR: m: 6.4 mg/day, f: 5.7 mg/day)	Selenium [µg/day] (EAR: m: 35 µg/day, f: 30 µg/day)	Iodine [µg/day] (EAR: m, f: 100 µg/day)
	m/f	m/f	m/f	m/f
Germany	53/60	8/13	n.d.	43/53
Ireland	61/68	14/13	n.d.	18/21
Denmark	64/61	10/10	16/15	7/12
Finland	25/33	7/10	12/13	9/9

2.2. Recommended dietary allowances (RDA)

If a standard deviation (SD) of the EAR exists and the nutrient requirement follows a Gaussian symmetric distribution, the RDA is set at two SD above the EAR (RDA = EAR $+2SD_{EAR}$). In cases where a SD is not available a coefficient of variation (CV) of 10% is used and the RDA is calculated by adding two CV (RDA = 1.2 × EAR). Using that calculation based on normal distribution around 97.5% of the population should have an adequate intake if the RDA is met.

However, most of the EAR values were calculated in very small studies. Some of them were undertaken > 50 years ago. In the meantime, the available food and the dietary habits have substantially changed. Consequently, the EAR might be higher or lower. In addition, many of the EAR are based on food composition data collected > 40 years ago. The available food and dietary composition, however, has substantially changed since then. If the special need of different micronutrients within the life cycle is discussed, this uncertainty must be considered. In addition, the requirements of different age groups are extrapolated from the existing EAR values.

If a RDA cannot be determined, the so-called adequate intake (AI) is used which should be based on observed or experimentally determined approximation or estimates of nutrient intake by a group of healthy adult people that are assumed to be adequate.

Despite this more or less rough estimations of micronutrient requirements these data must be used to calculate the extent of adequacy or inadequacy. However, we must consider that typical deficiency signs represent an end stage disease which develops over a more or less long time period. These unspecific changes are defined as hidden hunger.

2.3. Micronutrient deficiency and hidden hunger

A real micronutrient deficiency with classical clinical symptoms such as scurvy, rickets or anemia can be defined as an end stage disease. End stage is the final disease state of a progressive disease, e.g. chronic kidney disease (CKD) leading finally to hemodialysis. But before the kidney develops complete loss of function different stages of a CKD (1 to 5) occur. Without the technical possibilities of hemodialysis the final stage of CKD will ultimately lead to death. Similarly, the final stage of many micronutrient deficiencies leads to death. < 100 years ago vitamin B12 deficiency or scurvy were lethal diseases. The discovery of the basic causes of the diseases and the ability to synthesize micronutrients helped to cure these end stage diseases. Consequently, it was accepted that specific micronutrients are only needed if clinical signs of a typical deficiency occur. However, the fact that an end stage disease might have a time period of progression and might run through different stages was overlooked. This is the reason why the term hidden hunger was defined and is now generally accepted [7]. Because the EAR is the point were 50% are at risk and the other 50% are not at risk to develop a real deficiency, this point can be used as value defining the area of hidden hunger (depending on the demand, age, gender and further variables). Fig. 2 refers to the relationship of requirement and development of clinical deficiency. If the requirement is achieved up to 100% there should be neither hidden hunger nor any kind of micronutrient related disease.

Along with decreasing adequacy of the micronutrient supply unspecific symptoms can occur which usually are not detected via blood levels of the micronutrient in an early stage with only few exceptions (e.g. vitamin D). For example the blood level of vitamin A (retinol) is strictly regulated on a constant level until the liver, the main storage organ is depleted. At this point, the first signs of vitamin A deficiency occur (night blindness) followed by changes of the eyes (Bitot's spots, keratomalacia) leading finally to blindness. Other examples are illnesses such as anemia and rickets. Usually a long time before respiratory tract infections occur an anemia is present. Rickets is the end stage of vitamin D deficiency in children and osteomalacia in adults. Rickets was the main cause leading to an increased childhood mortality from the 19th until the mid of the 20th century, the period during which vitamin D was discovered. Rickets was frequently associated with another disease: tuberculosis. Ancient treatment of tuberculosis

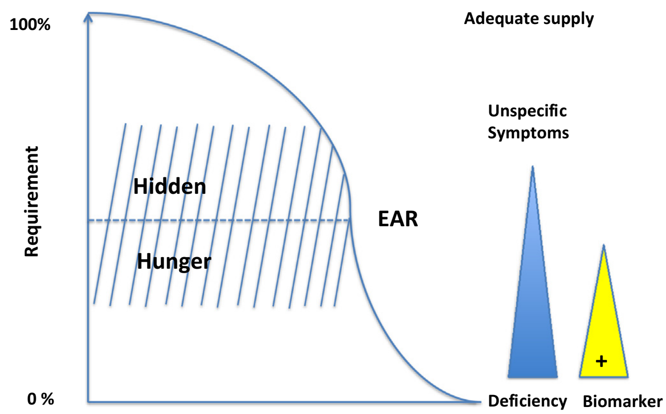

Fig. 2. Hidden Hunger definition related to increasing inadequacy of micronutrient supply above or below the EAR. Specific biomarkers indicating a deficiency are in most cases only valid when the supply is declining to cero. Source: [8].

with natural sunlight improved at least both, rickets and tuberculosis. In 1994, the reason for this combination was found: vitamin D is necessary for the formation of an endogenous defensin (cathelicidin) which acts like an antibiotic against tuberculosis bacteria. Both, vitamin D and vitamin A are important for the mucosal barrier and the immune system in the respiratory tract. This might explain why a consequent supply of raw cod liver oil, which is rich in vitamin D and vitamin A, to children (e.g. in Scandinavia) reduces the number and severity of respiratory tract infections. There is indeed good evidence from clinical studies that raw cod liver oil (not purified) reduces incidence of upper respiratory tract infections in children due to increased defensine and cathelicidine expression [9,10].

Vitamin D deficiency in adults results in a painful demineralization of the bones increasing fragility and resulting in spontaneous fractures. Before the demineralization becomes visible, diffuse pain sensations exist which are usually not diagnosed as vitamin D deficiency. Frequently, the diagnosis of fibromyalgia is made to describe the muscle weakness and chronic pain. Very recently, a meta-analysis has described a strong relationship between a hypovitaminosis D in patients with the so-called chronic-widespread pain (CWP) [11]. Indeed, treatment of CWP with vitamin D reduced pain and increased quality of life [12].

As an end stage vitamin B12 deficiency results in funicular myelosis, but megaloblastic anemia with consequences on human health develops a long time before. Today we know, that both illnesses belong together and that they have their origin in vitamin B12 deficiency. This allows us to treat vitamin B12 deficiency before the development of an end stage disease. There are only few examples in which we can detect signs of the progressive development before an end stage disease can be diagnosed. For example, early pathophysiological alterations of tissues, e.g. endothelial cells, might occur due to a hidden hunger of either vitamin E or vitamin K2. In both cases, an optimum intake (RDA or more) with the diet was related to a lower incidence of cardiovascular diseases [13,14].

In most cases of clinical deficiencies, we do not have any biomarker and with regard to a couple of micronutrients we even do not have clear symptoms of a clinical end stage (e.g. chromium, molybdenum, pantothenic acid, vitamin E). As long as we cannot rule out hidden hunger, we should carefully look whether the recommended intakes are achieved. An intake below the recommendation might be without consequences, depending at least on the time period and the percentage of the reduced intake. However, an intake below EAR increases by definition the development of a deficiency and therefore strategies to improve the supply are needed. This is of particular interest in healthy groups which may have a higher need for selected micronutrients or a lower supply due to life style or age. Based on current studies different inadequacies of micronutrients might exits in specific healthy age groups.

3. Literature search and study selection

The following life cycle related discussion of adequate or inadequate micronutrient supply is based on a narrative literature review (see Supplementary material). The literature search was restricted to the time period 2010–2017.

To uncover studies reporting life cycle issues related to micronutrients, we reviewed different databases (i.e., Medline, Embase, Cochrane Database of Systematic Reviews), as well as the Internet and different library catalogues and document servers of the University of Hohenheim.

The study selection was carried out independently by two nutritionists and the results of our selection was compared with the independent search.

Summarizing the potential different micronutrient inadequacies within different groups needs to consider a couple of special features related to country dependent differences of dietary diversity, income, traditions and presence of food fortification. In many studies, only the intake of selected micronutrients was estimated. Consequently further inadequacies might exist which not addressed within these studies.

3.1. Adolescents

Adolescents are a vulnerable group with respect to adequate nutrition. They tend to follow trends and modern life style circumstances that might question a healthy nutrition. According to a recent study and based on different questionnaires, European adolescents consume a diet, which contains half of the recommended amount of fruit and vegetables and less than two thirds of the recommended amount of milk and milk products [15].

Our study of the literature showed 25 original articles, seven reviews and two guideline articles. The overall results with respect to micronutrient inadequacies were in line with the results of the German National Consumption Survey II (NVS-II) [16]. The most critical micronutrients were vitamin D, folate, calcium and iron. Few studies also showed inadequacies with respect to vitamin E, vitamin C and different trace elements. A low supply of vitamin C or vitamin E usually depends on differences in regional dietary diversity and therefore a general statement with regard to the supply of these vitamins is not advisable. Only few studies exist, which show an inadequate supply of these vitamins. However, iron, iodine, vitamin D and folate seem to be a worldwide problem in low- as well as in high-income countries.

3.1.1. Iron

Iron is the most critical micronutrient worldwide. Iron inadequacy and deficiency is present in high- as well as in low-income countries, however, not only in adolescents. Intakes below the RDA in adolescents occurred between 91% and 5% in-high income countries. In studies from low-income countries, anemia rates in adolescents ranged from 20% to 40%, reflecting iron deficiency (ID). A recent European study concluded: “On the basis of WHO guidelines 2012 for the interpretation of the iron status data at population level, the results indicate that, in the European context, ID is not prevalent neither in boys nor in girls, and that iron depletion is prevalent in girls but not in boys. Adolescent girls therefore constitute a group at risk of ID, and specific attention should be given to them during adolescence to ensure that their dietary intake of iron is adequate to their requirements” [17,18].

Indeed, the data from the NVS-II clearly show that female adolescents and adults up to the age of 50 have a serious problem to achieve an adequate iron supply. They do not even reach 75% of the reference value (calculated as median) of the RDA. Due to the increasing number of females practicing a vegetarian or even vegan diet the overall supply of female adolescents and adults will become worse.

3.1.2. Iodine

Europe and Africa are the regions with the highest number of moderate and severe iodine deficiency. Despite the fact that salt is fortified with iodine there seems to be an increasing number of iodine deficient people. Looking at the data of the NVS-II [16] the problem is obvious: adolescents and young adults, in particular females, will not achieve a sufficient iodine intake, even not with fortified salt because of the recommendations to reduce salt intake. Furthermore, the rising consumption of "trendy salt" (e.g. crystal salt from the Himalayas) will additionally decrease iodine intake. The exclusion of iodized salt from the diet will result in an iodine supply below 50% of the RDA, the consumption of iodized salt has the effect that around 80% of the RDA can be reached.

3.1.3. Vitamin D

Vitamin D inadequacy is an emerging global problem. Even vitamin D deficiency diseases are no longer visible to a greater extent in high-income countries, there is evidence that a moderate deficiency may have a strong impact on general health in particular in pregnancy and elderly. The fact that the problem has not been realized up until recent years is related to the observation that the 25(OH)D and not the 1,25(OH)$_2$D plasma level reveals a clear relationship between plasma level and status. This has been elucidated in the last 10 years. Studies on adolescents and vitamin D supply (n = 11) clearly show that this seems to be a problem of high-income countries, in particular those without food fortification (e.g. Germany), which is also present in Asia and Africa [19].

The NVS-II documented that all age groups only achieve 40% (females) or 50% (males) of the RDA (5 μg). Thus, the dietary supply is far below the recent recommendation of the German Association for Nutrition (DGE) (20 μg/day). The reason is the rare consumption of fat fish, and dried mushrooms which are the only dietary sources of vitamin D. The impact of vitamin D synthesis in the skin following sun exposure depends on the season and will be critical during late autumn, winter and fall.

Adolescents are claimed to be a population group with high prevalence of vitamin D deficiency and inadequacy even in Northern America. Vitamin D intakes between 10 μg/day to 30 μg/day are required by white adolescents during winter to maintain serum 25(OH)D concentrations > 25 to 50 nmol/L.

Regarding the definition of adequacy, three cut off plasma levels are used:

25(OH)D plasma levels < 30 nmol/L (< 12 ng/ml) are defined as insufficient, and < 50 nmol/L (20 ng/ml) as moderate insufficient. Other official definitions (e.g. Robert Koch Institute) define levels < 30 nmol/L as deficient, and < 50 nmol/L as insufficient. After an ongoing debate, the US American Institute of Medicine (IOM) considers insufficient or inadequate at levels < 50 nmol/L. The 25(OH)D level reflects total intake of either vitamin D2 or D3 and the cutaneous synthesis. Therefore, the plasma level is the best indicator to define the vitamin D status.

The prevalence of deficient or insufficient vitamin D status in adolescents is highest in European countries (15%) and Saudi Arabia (females, 81%). However, the prevalence of moderate insufficiency worldwide is between 30% to 40%, with the exception of Mexico (8%). Even fortification of dairy products, e.g. in the US, will not ensure sufficiency. A Canadian study with adolescent males and females (3–18 years) detected 71% of this population group showing a sufficient level (> 50 nmol/L) and 5% to 6% showing a deficient level (< 30 nmol/L) of vitamin D [19].

3.1.4. Folate

Folate belongs to the critical vitamins worldwide and its dietary supply depends on the bioavailability from its food sources. Folate from plant-derived food sources has a lower bioavailability than from animal-derived food sources. This is due to the fact that folate from plants is a polyglutamate which needs to be metabolized (deconjugated) in the intestine, whereas animal-derived folate is a monoglutamate which can be directly absorbed. In cases of prospected pregnancy, a folate supplement is strongly recommended. However, data on folate adequacy or inadequacy are scarce. In the HELENA trial, vitamin status was determined on the basis of blood levels [15]. Insufficient concentrations in the blood were identified for vitamin D (75%), vitamin B6 (20%) and folate (35%). Deficient levels were detected for folate (15%), vitamin D (15%), β-carotene (25%), vitamin B6 (5%) and vitamin E (5%).

Looking again on the NVS-II, the data show an inadequate supply of both men and women, reaching only 60% (females) and 70% (males) of the recommendations for folate. These data are based on a recommendation of 400 μg/day. After completion of the NVS-II, the recommendation was lowered to 300 μg/day. The estimates of the above mentioned reference values of the RDA for folate didn't take into account the difference in bioavailability different food sources.

3.1.5. Conclusion

There is good scientific evidence that adolescents, in particular females, may have an inadequate supply with vitamin D, folate, iron and iodine. A real deficiency might be rare, but inadequacy might have an impact on health, in particular if the need for vitamin intake increases, e.g. during pregnancy or as a consequence of a disease.

3.2. Pregnant women

To achieve an adequate supply of essential micronutrients a mixed diet with an adequate energy intake should be sufficient [20]. Such a balanced diet is accessible for the European population but some groups may be at risk for an in adequate intake. In particular iron, folate, vitamin D and vitamin B12 are affected. Pregnant women belong to a vulnerable population.

For example, a study in Hackney, London – the region with the highest incidence of low birth weight (LBW) infants in England and Wales – showed that 78% of mothers had an inadequate diet that met fewer than four of 16 dietary reference intake values [21]. Within a follow-up for nine months it has been shown that in a group of non-supplemented women with a more or less poor diet folate and ferritin were critical low. The risk of giving birth to a small-for-gestational age (SGA) child was fourfold for this group.

During the childbearing period, females are often not sufficiently supplied with all water-soluble vitamins. Micronutrient deficiencies or suboptimal/inadequate intakes may be associated with increased reproductive risks, ranging from infertility to fetal structural defects and long-term diseases [22,23]. The reasons for inadequate intake are manifold: poor knowledge regarding adequate nutrition; special diets aimed at avoiding excessive weight gain; "healthy" vegetarian or even vegan diets; problems with eating (nausea, vomiting); and misinformation regarding specific nutrients (e.g. vitamin A). Further aspects interfere with the adequacy of micronutrient supply during pregnancy, such as maternal age, clothing, environment, geography and at least socioeconomic status (SES) [5].

3.2.1. Critical micronutrients during pregnancy

Inadequate supply of several micronutrients has an impact on fetal development (Table 4). The prevalence and consequences of inadequate micronutrient supply have been reviewed recently.

Malnutrition during pregnancy, and in particular poor micronutrient intake, are general risks for a SGA newborn.

3.2.2. Folate

There is good scientific evidence that adequate supply of folic acid is of critical importance with respect to the protection against neural tube defects (NTD) [25]. Estimated folate requirements increase by 50% to

Table 4
Micronutrient inadequacy and impact on fetal development.
Source: [22,24].

Micronutrients	Developmental problems with low intake
Vitamin B2, niacin	Risk of malformations of the urogenital tract
B-vitamins	Risk of malformations of the cardiovascular system
Vitamin B12, vitamin B6	Preterm birth
Iron, magnesium, niacin	2 to 5 fold higher risk of NTD
Zinc	Higher NTD risk
Iron, magnesium, vitamin C	Lower risk of cleft formation
Folate	Four-fold higher risk of NTD
Vitamin A	Risk of inadequate lung maturation, in particular in preterm birth
Iodine	Low birth weight

Abbreviations: NTD: neural tube defect(s).

600 μg during pregnancy. Even though a small quantities can provide adequate amounts of folate, the poor bioavailability of folate limits an adequate supply. Moreover, in most countries, females do not even reach the recommendations for non-pregnant women. Periconceptional supplementation of 400 μg/day of folic acid is recommended for the prevention of NTD.

3.2.3. Iron

Neonates just after birth have a total body store of about 1 g of iron. This total amount of iron has been provided by the mother during pregnancy. However, the mother also has to provide about 400 mg from her own hepatic stores to the newborn after birth. Thus, extra iron is required for the placenta and the growing fetus. In addition, the expansion of maternal red cell mass and blood loss during delivery needs iron [26]. Inadequate iron reserves or iron-deficiency often exist before pregnancy. Maternal iron deficiency anemia (IDA) may be aggravated during pregnancy, as fetal iron metabolism depends completely on maternal metabolism [27]. Iron status seems to interfere with pregnancy disorders such as preeclampsia and with inappropriate catch-up growth [28].

Iron deficiency anemia should be prevented and treated. Screening of ferritin levels in early pregnancy may help to identify women who may benefit from iron supplementation. The increased iron absorption during pregnancy, coupled with the mobilization of iron stores, may be sufficient in women with high iron stores, who may not need iron supplements.

3.2.4. Vitamin A

Vitamin A is obtained from the diet either as pre-formed vitamin A in the form of retinol or retinyl-esters, or as provitamin A-carotenoids. The highest content of preformed vitamin A is found in liver and liver oils of marine animals. Yellow and green leafy vegetables provide different amounts of provitamin A [29]. However, high doses (> 6 mg/day) of the provitamin A are needed to reach the recommended dietary intake of 1000 μg retinol/day [30].

The American Pediatric Association cites vitamin A as one of the most critical vitamins during pregnancy and the breastfeeding period, especially in terms of lung function and maturation [31]. If the vitamin A supply of the mother is inadequate, her supply to the fetus will also be inadequate, as will later be her milk. These inadequacies cannot be compensated by postnatal supplementation. Despite the fact that food rich in vitamin A and beta-carotene is generally available, risk groups for low vitamin A supply do exist in the western world [30]. In a group of females with either gemini or short birth rates it became evident, that intake of preformed Vitamin A was below recommendations and as the consequence low plasma retinol levels were detected in mothers and retinol levels in the umbilical blood within the deficiency range [32]. In case of preterm birth newborns are at risk for inadequate lung maturation and subsequent broncho-pumonary disease [33].

3.2.5. Vitamin D

Given the evolving concept of vitamin D sufficiency, it is currently believed that sufficiency may be defined as serum 25(OH)D levels > 75 nmol/L. The current prevalence of vitamin D insufficiency during pregnancy is estimated as high as 70% in western countries if insufficiency is defined as a 25(OH)D concentration below 75 to 80 nmol/L [34]. Maternal vitamin D deficiency predisposes newborns to neonatal hypocalcemia, and subsequently to rickets. Observational studies also document that the bone mass of the newborn is related to the vitamin D status of the mother [35].

Based on different studies, vitamin D deficiency during pregnancy impairs brain development in the offspring and leads to changes which persist in the adult brain [36]. Based on a recent meta-analysis, the risk of type 1 diabetes is significantly reduced in infants who were supplemented with vitamin D [37]. It is suggested that vitamin D supplementation in early childhood may protect against the development of type 1 diabetes. The data available to date suggested that vitamin D deficiency during pregnancy is not only linked to maternal skeletal preservation and fetal skeletal formation but may also affect maternal outcomes and fetal imprinting [38].

3.2.6. Iodine

Approximately half the European population still suffers from an inadequate iodine supply. Low urinary iodine excretion is especially common among pregnant women and school children. The World Health Organization (WHO) recently increased its recommendation for iodine intake during pregnancy and lactation from 200 to 250 μg/day and suggested that a median urinary iodine concentration (UIC) of 150 to 250 μg/L indicates adequate iodine intake [39]. WHO recommends iodine supplementation in pregnancy only in countries where < 90% of households use iodized salt or where the median UIC in schoolchildren is below 100 μg/L. However, different national surveys in the USA and Europe document that even when iodized salt is consumed, this might not be enough to cope with the increased iodine demand during pregnancy. Iodine supplementation (150 μg/day) has been recommended in the case of pregnancy [40].

Iodine is involved in nerve development, as well as thyroid follicle growth and the synthesis of thyroid hormones (THs), which are of essential importance for the development of the fetal central nervous system [41]. Pregnant women with an UIC below 50 μg/L during the third trimester were significantly more likely to have an SGA infant with a lower mean birth weight than women with an UIC between 100 and 149 μg/L. Higher TSH levels were also associated with a higher risk of having an SGA baby or a LBW newborn. The later mean intelligence quotient (IQ) of children born to women with an UIC below 50 μ/L was found to be significantly lower compared to controls with adequate iodine supplementation [42]. Recent cross-sectional studies performed in several European countries revealed a median UIC in pregnant women in the range of 95 to 130 μg/L [39,43]. Half the women had an UIC below 100 μg/L and about a quarter showed concentrations below 50 μg/L, indicating a maternal iodine status associated with moderate or severe iodine deficiency, respectively, in the offspring.

3.3. The first 1000 days: a developmental window which might be irreversibly closed

Adequate nutrition in particular adequate micronutrient supply during pregnancy is a prerequisite for fetal development and later life of the child. Intra uterine growth retardation (IUGR) may be taken as a phenotype of poor diet quality during pregnancy. The phenotype of IUGR is low birth weight of the newborn. Newborns with low birth weight at birth (< 2500 g) have a four times risk to die during their first 28 days of life than those weighing between 2500 g and 2999 g, and a 10 times risk to die than newborns weighing between 3000 g and 3499 g [44]. But behind this phenotype also organ growth and development is reduced. This and further reasons may explain the increased

Table 5
Impact of selected nutrients on brain development.

Nutrient	Requirement	Brain area
Iron	Myelin formation	White matter
	Monoamine synthesis	Striatal frontal
	Neuronal and glial energy metabolism	Hippocampal-frontal
Iodine	Myelination, neuronal proliferation	Cortex, striatum
		Hippocampus
Zinc	DNA synthesis	Autonomic nervous system
	Neurotransmitter	Hippocampus, cerebellum
Copper	Neurotransmitter synthesis, energy metabolism	Cerebellum
Vitamin A	Neurogenesis	Hippocampus
	Neurotrophic factors	
Vitamin D	Neurogenesis	Hippocampus
	Neurotrophic factors	White matter
LC-PUFA	Synaptogenesis	Eye
	Myelin	Cortex

Abbreviations: LC-PUFA: Long chain polyunsaturated fatty acids.

risk of the offspring for later non-communicable diseases (NCD), e.g. hypertension and diabetes [45].

3.4. Micronutrients and brain development

If malnutrition persists after birth, normal brain development may be impaired. There is good scientific evidence that certain micronutrients – in particular iron, iodine, zinc, folate, vitamin A and vitamin D – are critically involved in pre- and postnatal brain development. These micronutrients are the major missing nutrients, whether isolated or in combination, in the diet of one-third of the world's population. Further micronutrients, proteins, energy and n-3 fatty acids may also have an impact on brain development.

Table 5 summarizes the specific brain-related micronutrients and their impact on brain development during the late fetal and neonatal period. The magnitude of any impairment of brain development and at least the effect on brain function depends on the severity of the micronutrient deficiency. In many cases, deficiencies do not exist in isolated forms. Other micronutrients may also be involved, depending on the food pattern, as well as protein-energy malnutrition which might also play a role. The latter has also a negative impact on brain development, but will not be discussed further in this chapter [46].

3.4.1. Iron

A couple of studies from low-income countries document the importance of micronutrients for brain development. A review discussing 14 different studies has shown associations between iron deficiency anemia and poor cognitive and motor development as well as behavioral problems [47]. Longitudinal studies consistently indicate that children who are anemic during infancy continue to have impaired cognitive abilities, achieve bad school performances, and have more behavior problems during middle childhood [47].

3.4.2. Iodine

WHO considers iodine deficiency to be “the single most important preventable cause of brain damage” worldwide. Approximately one-third of the world's population is estimated to have insufficient iodine intake, in particular in Southeast Asia and Europe [48]. Adequate maternal iodine stores within the thyroid are important for normal fetal and infant neurodevelopment. Adequate thyroid iodine stores (in iodine-sufficient regions) ensure the increased demand for iodine during pregnancy if optimal intake is maintained. In iodine-deficient regions, however, potentially inadequate iodine stores are rapidly depleted during pregnancy, putting the fetus at risk of developmental impairment, especially of the brain. In particular, the severity of cognitive impairment seems to be associated with the degree of iodine deficiency [49]. In early childhood, iodine deficiency impairs cognition, but in contrast to fetal iodine deficiency, there is evidence of improvement with iodine treatment. Children from iodine-deficient areas had more cognitive impairments compared with children from areas with sufficient iodine [50]. Several European studies have shown that isolated iodine deficiency during pregnancy is associated with impaired cognitive development in children [46]. In an elegant study, it has been shown that poor iodine intake of the mother correlates with poorer neurodevelopment at the age of 3 of the child [51]. In 33,047 mother-child pairs, excluding iodine supplement users, maternal iodine intake was associated with child language delay ($P = 0.024$), externalizing and internalizing behavior problems (both $P < 0.001$), and fine motor skills ($P = 0.002$), but not gross motor skills or the risk of not being able to walk unaided at 17 months of age. In 74% of the participants who had an iodine intake < 160 mg/day (EAR), suboptimal iodine intake was estimated to account for 5% (95% CI: 25%, 14%) of the cases of language delay, 16% (95% CI: 0%, 21%) of the cases of externalizing behavior problems > 1.5 SD, and 16% (95% CI: 10%, 21%) of the cases of internalizing behavior problems > 1.5 SD. In 48,297 mother-child pairs, including iodine supplement users, no protective effects of supplemental iodine during pregnancy on neurodevelopment were found.

In a recent observational trial in the UK, the effect of inadequate iodine status in 14,551 pregnant women on the cognitive outcome of their children (13,988) was evaluated. The results support the hypothesis that inadequate iodine status during early pregnancy is adversely associated with child cognitive development. Low maternal iodine status was associated with an increased risk of suboptimum scores for verbal IQ at age eight, and reading accuracy, comprehension, and reading score at age nine [52].

Based on different intervention studies in children at different ages, it is argued that the developmental effects of iodine deficiency during early gestation are irreversible despite later iodine repletion. Supplementation of pregnant women, however, showed a clear benefit on cognitive outcome of the children. In iodine-insufficient areas of Spain, the effect of a supplementation during pregnancy on cognitive development of the offspring (aged three months to three years) has been well documented in three out of four studies [53].

3.4.3. Vitamin D

Vitamin D deficiency is observed in 60% of Caucasian women and also in women with dark skin, where the rate is estimated to be even higher [54]. Maternal vitamin D deficiency during pregnancy has frequently been described as associated with adverse health outcome of the offspring, including intrauterine growth restriction and impaired bone mass. Vitamin D deficiency is also related to various cognitive and behavioral dysfunctions, e.g., schizophrenia [55]. Infants born to mothers with vitamin D deficiency had significantly lower birth weights and an increased risk for being too small for gestational age compared with infants born to mothers with adequate plasma levels as a sign of vitamin D sufficiency [56]. Low maternal serum vitamin D levels during pregnancy of 743 Caucasian women in Australia were significantly associated with offspring language impairment at five and 10 years of age [57]. Besides its well-known actions on bone and the immune system, vitamin D seems also important in the developing brain, controlling the gene expression of so-called neurotrophins, which are important for neurogenesis [53].

3.4.4. Prevention of micronutrient gaps

In case of pregnancy, it was recommended to take a folate/iron supplement. However, different studies showed that a multivitamin/mineral plus iron and folate seems to be better.

In the meantime, different meta-analyses including a recent Cochrane report have led to the recommendation of a multivitamin/mineral supplement plus iron and folate [58–60]. These metaanalyses clearly have documented that a multivitamin/mineral (MVM) is superior over the usual recommended iron + folate only supplementation.

Table 6
Meta-analysis addressing the impact of MVM supplementation on malformations.
Source: [62].

Malformation	Risk reduction (OR/95% CI)* MVM Supplement	Study type
NTD	0.67 (0.58–0.77)	Case Control
	0.52 (0.39–0.69)	Cohort and RCT
Cardiovascular	0.78 (0.67–0.92)	Case Control
	0.61 (0.40–0.92)	Cohort and RCT
Limb	0.48 (0.30–0.76)	Case Control
	0.57 (0.38–0.85)	Cohort and RCT
Cleft palate	0.76 (0.62–0.93)	Case Control
	0.42 (0.06–2.84)	Cohort and RCT
Cleft lip	0.63 (0.54–0.73)	Case Control
	0.58 (0.28–1.19)	Cohort and RCT
Urogenital	0.48 (0.30–0.76)	Case Control
	0.68 (0.35–1.31)	Cohort and RCT
Hydrocephalus	0.37 (0.24–0.56)	Case Control
	1.54 (0.53–4.50)	Cohort and RCT

A significant reduction of low birth weight and SGA was evident as well as a reduction of malformations (Table 6). The Cochrane meta-analysis, which reviewed data from high- and low-income countries concluded, that “Overall, pregnant women who received MVM supplementation had fewer low birth weight and SGA babies” [59]. A further meta-analysis which only reviewed studies from high-income countries (HIC) concluded: “Routine multivitamin use in HIC can be recommended” [61]. This kind of a more general recommendation considers that we do not really know which micronutrient gap might exist.

Prenatal supplementation with a multivitamin/mineral supplement does indeed reduce malformations. It also increases birth weight and reduces the incidence of SGA newborns [56]. Based on these findings, the Canadian Society of Obstetricians and Gynaecologists makes the following recommendations:

- In case of planned pregnancy, healthy females should take a multivitamin/mineral supplement containing folate (0.4–1.0 mg) on a daily basis.
- Females with specific risks (BMI > 35, diabetes, history of a child with NTD) are advised to take folate (5.0 mg) together with an multivitamin/mineral supplement two to three months prior to conception and up to 12 weeks after delivery.

3.4.5. Conclusion

The recommendations for pregnant women are not achieved in many cases. Folate, iron and vitamin D intakes are not sufficient, according to the recommendations [63]. In particular, in adolescent pregnancy, a poor micronutrient status becomes evident and increases the risk for SGA births [64]. The problem may become extended in case of vegetarians or vegans.

Micronutrients play an important role during different time periods of pregnancy. Even prior conception, an inadequate supply might affect fetal growth and outcome after birth. Based on different meta-analyses including Cochrane data, a multivitamin/mineral supplement containing folate and iron can be recommended in case of desire to have a child. Folate and iron, as frequently recommended alone, may not be sufficient.

3.5. Elderly

Malnutrition in the elderly is present in all over Europe and the number of malnourished elderly increases with age. Hundreds of articles are publishes on a regular base in scientific and public media, but most of them define malnutrition as an inadequate intake of energy leading to a progressive weight loss. Malnutrition is defined using different tools such as Malnutrition Assessment or Subjective Global Assessment and others, methods which calculate weight development and some subjective data, but do not calculate or evaluate micronutrient supply. In general, it can be argued that a (quantitative) malnutrition not necessarily leading to weight loss is also accompanied by a (qualitative) malnutrition. The quantitative malnutrition due to a poor protein intake results in a loss of muscle mass (sarcopenia) which might be overlooked due to the fact that a weight loss might not occur (sarcopenic obesity).

There is a general recommendation from different nutrition societies (German Society of nutrition, American Nutrition Society) to increase the offer food with a high concentration of micronutrients (quality) for elderly and to lower the offer of food high in energy (quantity).

There is an increasing number of studies documenting the inadequacy of micronutrient supply in elderly. Recently, a meta-analysis summarized the data from 41 studies which showed that, depending on the special micronutrient, between 15% and 90% of elderly were at risk for deficiency [65]. The risk was calculated for elderly who were below the EAR. Consequently, according to the definition of the EAR, those elderly were at risk for developing a deficiency with clinical consequences if they remain undersupplied. In particular, if the vitamin B supply is inadequate, this may be harmful for cognition and mood. > 30% of elderly were below the EAR for thiamin and riboflavin. 90% were below the EAR for Vitamin D and even for other vitamins, such as vitamin A, vitamin B6, folate, vitamin C and vitamin E, between 25% and 35% of the elderly were below the EAR. However, aside from the vitamins, also the mineral supply was below the EAR in a substantial part of the population. Around 70% were below the EAR for calcium and magnesium (men 73%, women 41%). An iodine intake below the EAR was evident in 20% of men and 26% of women.

The prevalence of malnutrition in elderly substantially increased in particular in the last 10 years in high-income countries. The problem of malnutrition is not only evident in elderly living in nursing homes, where between 20% and 60% are found to be more or less malnourished [66]. Malnutrition is also found in outpatients with a high prevalence (up to 60%). The reason for malnutrition, in particular for hidden hunger, among those elderly is the decreasing energy need as a result of a decrease in lean body mass, starting around the seventh decade. However, despite this reduced energy need, the need for micronutrients is in no way altered by this.

Different aspects are important to understand malnutrition in elderly:

- Decreased total food intake due to limited olfactory and gustatory function
- Drug intake and impaired absorption
- Poor micronutrient density in high-fat and high-sugar food
- Poor dental status
- Poverty
- Social isolation and loneliness

The quality of diet determines survival and health status in free living elderly of an European population [6]. Especially both high plasma levels of beta-carotene (as a marker for vegetable intake) and alpha-tocopherol (marker for edible plant oils) are associated with lower mortality in the elderly [67]. Epidemiological studies have demonstrated that the prevalence of nutritional deficiencies rises with increasing age, in particular, deficiencies of antioxidants (beta-carotene, vitamin C, vitamin E, selenium and zinc) or vitamin B (folic acid, vitamin B6, vitamin B12). Deficiencies of micronutrients, however, may contribute to or even promote cognitive impairment. Consequently, it is suggested that a straightforward strategy to improve micronutrient status may improve cognition or delay the onset of mild cognitive impairment and at least Alzheimer dementia.

3.5.1. Vitamin B12

Vitamin B12 deficiency increases with age. The major reason is atrophic gastritis, which affects 10% to 30% of people over 60 years of age. Also acid-reducing drugs might affect the absorption of vitamin B12. In a study with 1996 institutionalized males and females, vitamin B12 deficiency has been described in 34.9% of the study participants [68]. The prevalence of B12 deficiency in people over 60 years of age has been described to be around 6%, but 16% showed critical low vitamin B12 blood levels [69].

3.5.2. Conclusion

Low intake of micronutrients is frequent in elderly. It depends on a couple of external and some internal factors, which contribute to the decline of an adequate micronutrient supply. Diseases, drug use, declining appetite, social isolation and decreasing cognitive function, all these factors together impair dietary quality and subsequently adequate micronutrient supply. Despite the fact that elderly need less energy due to declining energy expenditure, they need the same amount of micronutrients as 20 years or even more before. Many studies with elderly focused on two to three vitamins, in particular vitamin B12, vitamin D and vitamin B6 but overlooked the fact that a low intake of one micronutrient with the diet is accompanied by other low intakes of micronutrients present within that “inadequate” diet. A low intake or low plasma level, as far as plasma levels are convincing, are biomarkers for a specific diet, low in that biomarker. Focusing only on one vitamin or mineral overlooks the fact that a micronutrient never comes alone (in the diet). Consequently, supplementation of one micronutrient alone is only meaningful if there is a clear indication (e.g. an isolated deficiency disease).

4. Lifestyle related needs

4.1. Diet

Lifestyle trends preferring a diet without meat or meat-derived products may result in an increasing number of individuals with micronutrient inadequacies (Table 7). In particular, vegan and vegetarian diets will result in a low intake of different micronutrients due to poor bioavailability of some of them from plant derived food or poor concentration within that diet. Indeed, a deficiency might not be visible but declining stores may become a borderline risk in particular in cases of disease or higher need (e.g. pregnancy). Depending on half-life, body stores and type of diet, an increased risk for inadequate supply of micronutrients develops in different time periods.

4.2. Reasons for inadequacy and recommendation

The bioavailability of iron from a vegetarian diet lower than of a mixed diet. Therefore, the RDA for iron from a completely vegetarian diet according to the U.S. Food and Nutrition Board (FNB) should be adjusted as follows: 14 mg/day for men and postmenopausal women, 33 mg/day for premenopausal women and 26 mg/day for adolescent girls. For strict vegetarians also the zinc supply should be 50% higher.

Table 8
Percentage of vegans with intake of micronutrients below recommendations. Source: [70].

Level of veganism[a]	Thiamin	B2	Niacin	Folate	B12	Fe	J	Na	Zn
Strict vegans	9%	7%	33%	20%	92%	7%	98%	100%	15%
Moderate Vegans	8%	51%	8%	24%	95%	7%	100%	100%	26%

[a] Moderate vegans consume from time to time eggs and dairy products.

Depending on the micronutrient a different number of vegans do not reach recommendations even in high income countries such as Germany with a wide variety of vegan food (Table 8).

A Danish cohort of vegans showed a low supply of vitamin B2 and vitamin B12 despite claiming an intake of supplements [71]. Further micronutrients which were below recommendations in female participants were vitamin A, vitamin D, zinc, iron and iodine. A couple of studies exist which show that intake of some micronutrients is lower than recommended. If it is considered that bioavailability may play a crucial role and that during pregnancy the demand increases, a vegan diet may be a risky game with respect to health and later development of the child. An inadequate supply of folate and other methyl donors, e.g. vitamin B12, has a strong impact on placenta formation and epigenetic programming during the early implantation period and embryonic fetal development. Low iron, iodine and zinc usually lead to a reduction of fetal growth and brain development. Up to now, no studies are available addressing the impact of micronutrient inadequacy on vegan populations and pregnancy outcome with respect to epigenetic. A recent systematic review of nine studies estimating the intake of micronutrients and pregnancy outcome showed inconsistent results [72]. The authors concluded: "Within these limits, vegan–vegetarian diets may be considered safe in pregnancy, provided that attention is paid to vitamin and trace element requirements". The problem of this diet on neurodevelopment has been mentioned above and needs to be considered.

4.3. Exercise

There are no studies available dealing with moderate exercise and micronutrient requirments. Demand of micronutrients in exercise may depend on the type and duration of exercise. The Scientific Committee on Food (SCF) recently stated that physical activity levels and demand of micronutrients are directly associated. Some metabolic pathways involved in energy metabolism and repair mechanisms may be stressed in athletes and very active individuals. Exercise may increase the requirement due to increased turnover, accelerated metabolism, or loss of nutrients, e.g. through sweat.

Few vitamins (thiamin, riboflavin and vitamin B6) are related to energy and substrate metabolism and consequently, their supply should be adapted to energy expenditure. It is calculated that 0.5 mg thiamin are needed per 1000 kcal to balance the additional energy expenditure.

Table 7
Lifestyle trends in diet and associated critical micronutrients.

Diet	Food	Critical Micronutrients
Flexi-vegetarian	Low in meat, meat derived products and fish	Iron, zinc, vitamin D, depending on the frequency of meat and fish in the diet
Lacto-ovo-vegetarian	No meat, meat products, fish	Iron, zinc, iodine, vitamin D
Lacto vegetarian	No meat, meat products, fish and eggs and food with eggs	Iron, zinc, iodine, vitamin A, vitamin D, folate[a]
Ovo-vegetarian	No meat, meat products, fish, milk, milk products	Iron, zinc, iodine, calcium, vitamin A, vitamin D, vitamin B2, vitamin B12, folate
Vegan	No animal derived food	Iron, zinc, iodine, calcium, vitamin A, vitamin D, vitamin B2, vitamin B12, folate
Fructarian	No animal derived food, preferred raw or dried fruits, nuts and seedlings	Iron, zinc, iodine, calcium, vitamin A, vitamin D, vitamin B2, vitamin B12, folate

[a] Only if milk or other products are not fortified with folate.

Vitamin B2 is an important cofactor for glucose and fatty acids and at least energy metabolism. 0.14 mg/kJ or 239 kcal are recommended. Vitamin B6 which is needed for the metabolism of proteins and amino acids, is related to protein intake. 0.016 mg vitamin B6 per g protein are defined to be adequate.

The importance of the above mentioned vitamins for physical exercise is documented following reduction of intake of these vitamins in healthy men [73]. An eleven-week depletion of these vitamins significantly decreased working capacity by 12% and biochemical indicators of physical activity. Further studies with similar approaches showed that maximum work capacity strongly depended on an adequate supply of these vitamins. Furthermore, based on recently published articles the following micronutrients might become critical in athletes: vitamin D, folate, vitamin B6, iron, calcium, potassium, magnesium (see Supplementary Table 2). In the majority of the studies, an inadequacy of iron, in particular in females, as well as of vitamin D have been reported. In Canadian pre-adolescent athletes (14–18 years), intakes below the RDA occurred for iron (91%), folate (89%) and calcium (84%) [74]. Despite these results, the authors concluded that supplementation is unnecessary with the exception of vitamin D. However, this is a questionable recommendation. Low calcium and vitamin D intake usually results in a lower bone mineral density and increases the risk for early osteoporosis. Indeed, a higher risk for osteoporosis has been described in female athletes [75].

Low vitamin D status has been described in 13 studies (see Supplementary Table 2). It is generally recommended to evaluate the vitamin D status in athletes and to compensate a low status with supplements. A meta-analysis (23 studies with 2313 athletes) reached the conclusion that 56% of the study participants were insufficiently supplied with vitamin D [76]. Vitamin D supplementation in cases of low status (< 50 nmol/L) might have a positive impact on muscle function, but up to now, clear effects on physical performance have not been described yet. It is evident, however, to take the significant role of vitamin D (together with vitamin A) for the immune system into account.

4.4. Iron

Iron deficiency in athletes is frequent and relevant as all stages of iron inadequacy affect physical performance. However, the fact that athletes are familiar with the problem of iron deficiency may lead to the opposite, an iron overload (ferritin > 200 μg/dl) due to a "preventive" supplementation, which has been shown, for example, in 11% of male Ethiopian athletes [77]. Nearly 50% of female rhythmic gymnasts showed iron deficiency (ferritin < 20 μg/dl) which might be due to a strong diet in the pre-season [78]. Nevertheless, as stated by a Swiss consensus conference, iron inadequacy is indeed a problem in athletes. A specific treatment should follow established guidelines for athletes.

4.5. Conclusion

Athletes are at risk for inadequacy of a couple of micronutrients. The inadequacy depends on the kind of exercise, the strength and the location (indoor or outdoor) and its manifestation and consequences are different in males and females. Supplementation of athletes should follow established guidelines.

5. General conclusion

Micronutrients are essential components of the human diet and contribute to growth, development and performance. It is known that the functions and effects of micronutrients may be different within the life cycle and should be ensured by an adequate diet. Nevertheless, different micronutrients are not adequately supplied within the life cycle according to a couple of studies and meta-analyses. This may or may not have adverse health effects, depending on the importance of the micronutrient not adequately supplied in a certain stage of the life cycle.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nfs.2018.03.001.

Author agreement/declaration

All authors have seen and approved the final version of the manuscript being submitted. They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Declarations of interest

There's no interest or belief that could affect the objectivity of the authors.

Conflict of interest

There are no financial relations that affect the authors' view of the topic.

Funding source declaration

The corresponding author has been funded by PGT Healthcare CH1213 Petit-Lancy, Geneva Switzerland.

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