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Importance of micronutrients in lifespan development

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Abstract
Nature contains components in a variety of forms, and these elements are highly important for the body to carry out its various tasks. At the biological, chemical, and molecular levels, trace elements are crucial for cellular processes. These substances serve as cofactors for numerous enzymes, as well as stabilizing centers for the structures of enzymes and proteins, to mediate important biochemical events. A few trace elements regulate crucial biological processes by binding to the molecular site of the cell membrane receptors or by switching the shape of the membrane to block the entry of particular molecules. Trace element functions provide a dual duty. They are crucial for maintaining cellular structures at normal levels, but when they are lacking, they can activate alternative pathways and lead to illness. These trace elements can be estimated using various analytical techniques and have therapeutic importance.

Keywords: Trace elements, enzyme, proteins, cell membrane

Introduction
Fat, protein, and carbs are macronutrients that provide energy and essential components for maintaining the body's overall composition. This ongoing process of rebuilding and re-construction requires micronutrients to function. As a result, the demand for micronutrients will vary based on individual needs that are connected to the various metabolic states during the life cycle. The need for micronutrients is high throughout the first 1000 days of life, from conception until the end of the second year, and if the supply is inadequate, this might have an impact on physical and, at the very least, cognitive development. Micronutrients like iron and iodine in particular might be crucial at that time. The phrase "hidden hunger" has been coined to characterize this scenario since clinical signs of deficiencies take a while to manifest, yet inadequate supply of one or more micronutrients may have negative health effects. Pregnancy and the early years of life in particular are crucial, and hidden hunger, which affects over 2 billion people, predominantly women and children, is a global issue. Throughout the life cycle, the significance of several requirements is typically overlooked. In addition, we don't truly understand what each person needs. The assessment of the need is not supported by strong scientific technique or data, but rather research that calculate the supply of a micronutrient to prevent a deficiency illness in a population that is healthy. We must keep in mind that the supply may become crucial at various points in the life cycle, particularly in the event of an illness or an abrupt rise in metabolic turnover (Biesalski *et al*., 2018) [8].
Zinc, selenium, iron are crucial ingredients in enzymes because they draw or pull molecules and make it easier for them to change into particular end products. Redox processes, which generate and use metabolic energy and have an influence on the structural stability and the import of certain biological molecules, involve just a small number of components as donors or acceptors of electrons. In higher animals, iron is involved in the binding, transportation, and release of oxygen. By facilitating the binding of molecules to their receptor sites on cell membranes, by altering the ionic nature of the membrane to prevent or allow certain molecules to enter or leave a cell, and by inducing gene expression, which leads to the formation of protein involved in life processes, some trace elements regulate critical biological processes.
The elements that are important for the human body include the four basis elements C, O, N, H along with minor elements such as Mn, Fe, Co, Ni, Cu, Zn, Mo, Se, and trace elements including Na, Mg, K, Ca, S, P, and Cl. Other functional elements include Li, V, Cr, B, F, Si, As, however no specific function has been suggested for these elements.

Biological Classification of Trace Elements
Numerous writers have proposed different classifications of elements, including both major and trace elements, which are thought to be crucial for healthy development and growth.

According to the quantity detected in tissues,

Categorical Classification of Trace Elements

An adult human body is found to contain at least 29 distinct types of elements, both metal and nonmetal. These 29 components can be generally divided into the following five groups:

Group I: These substances make up the fundamental parts of macromolecules including lipids, proteins, and carbohydrates. These groupings' respective elements include carbon, hydrogen, oxygen, and nitrogen.

Group II: These minerals are crucial for nutrition. They are sometimes referred to as macro elements or major elements. For a mature person, their daily need is greater than 100 mg. In the absence of effective intervention, the absence of such components frequently proves deadly. These elements are calcium, phosphorus, magnesium, sodium, potassium, chloride, and sulfur.

Group III: There are the required trace elements. A trace element is one whose daily need is less than 100 mg and whose deficiency results in illnesses or is potentially fatal. Selenium, molybdenum, iodine, chromium, copper, iron, zinc, chromium, cobalt, and iodine are among these elements. Among them, iodine is a nonmetal, whereas the others are.

Group IV: They are additional trace elements. Although it's unknown what they do, they could be quite important. This group of elements includes cadmium, nickel, silica, tin, vanadium, aluminum, and silica.

Group V: Although this particular set of metals is not necessary, their presence might be hazardous. They are unknown to serve any purpose in the human body. This category includes the elements lead, cyanide, mercury, and gold.

Group III, often known as the minor elements, was among the trace elements. Their daily need is less than 100 mg, and while their absence would not interfere with normal growth, another metal could be able to perform their function instead. Metal content in human tissues and bodily fluids is measured using analytical techniques.

Table 1: Changing Nutrient Needs through the Life Cycle

Life Stage	Change in Nutrient Needs
Pregnancy period	Energy, protein, fatty acids, vitamins A, C, B (B1, B2, B3, B5, B6, B12, folate, and choline), calcium, phosphorus, magnesium, potassium, iron, zinc, copper, chromium, selenium, iodine, manganese, and molybdenum, are required.
Lactation period	Vitamins A, C, and E, all B vitamins, salt, and magnesium required while there is decreased need for iron
Infancy and childhood period	Calories, protein, and essential fatty acids are required
Adolescence period	Added needs for calories, protein, calcium, phosphorus, magnesium, and zinc (only for females)
Early adulthood (ages 19-50)	Vitamins C, K, B (B1, B2, and B3), choline, magnesium, zinc, chromium, and manganese, have higher needs for men than for women while iron is more required for women.
Middle age (ages 51-70)	Added need for vitamin B6, vitamin D
Elderly (age70+)	Increased need for vitamin D Reduced needs for energy and iron (only for females)

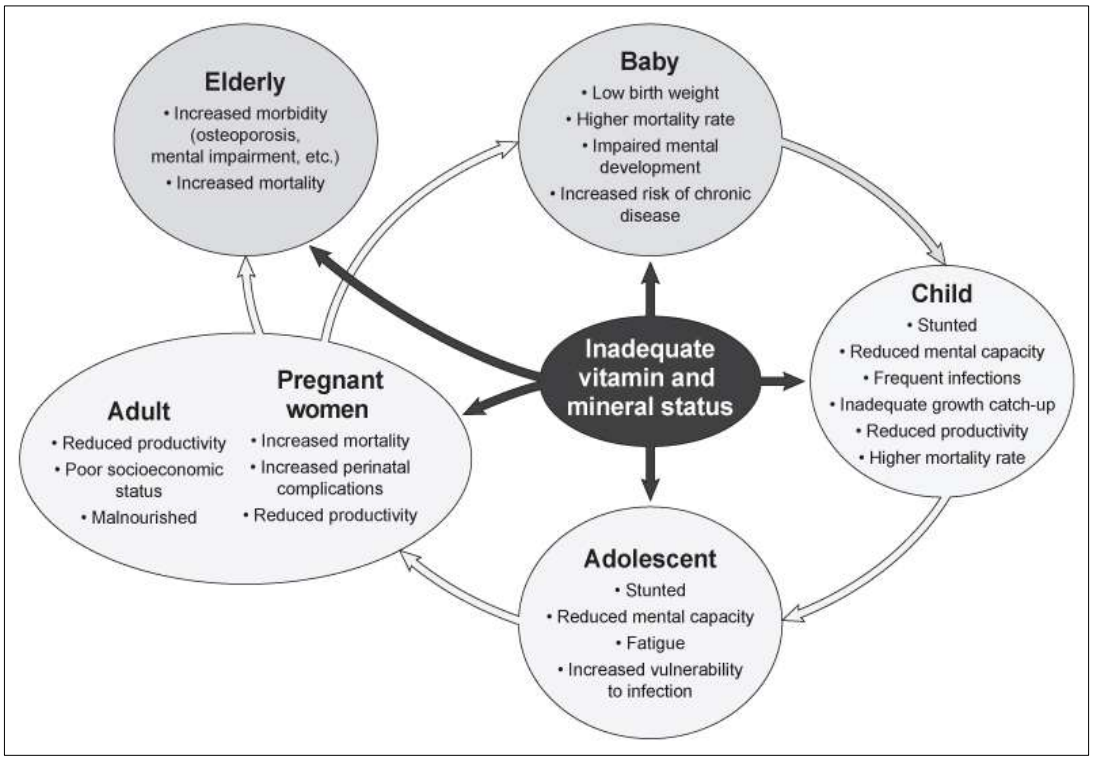

Fig 1: The cycle of micronutrient inadequacies across the life span

Brain Development in Humans

During prenatal and early postnatal development, nutrients and growth hormones control brain development. The rapidly developing brain exhibits its highest level of flexibility while simultaneously being more susceptible to food deficiency. The impact of some nutrients on brain development is higher than that of others. These consist of iron, zinc, copper, copper, iodine, selenium, vitamin A, choline, folate, certain fats, protein, and energy. The principles of timing, dosage, and duration will control any nutrient's impact on brain growth, whether it be a shortfall or an oversupply. Knowing which part of the brain is mainly impacted and having neurologic tests that focus on those regions' activities are necessary for being able to identify the precise consequences of nutritional deficits. For instance, iron deficiency in the newborn period affects the production of monoamine neurotransmitters, myelination, and hippocampus energy metabolism. Tests for processing speed (myelination), changes in motor and affective function (monoamines), and recognition memory (hippocampus) might all be used to evaluate these effects.

Different areas and functions of the brain grow at various stages during the temporally prolonged and complicated process of brain development (Grossman *et al*., 2003) [7]. The anterior-posterior and dorsal-ventral axis of the neural tube have already formed in humans 5 weeks after conception (Levitt, 2003) [12]. From 8 to 16 weeks of gestation, the cortical plate, the precursor of the cerebral cortex, and some interneuronal connections develop (Levitt, 2003) [12]. Between 24 weeks of pregnancy and neonatal period, the cortical plate's neurons die and are replaced by more advanced cortical neurons. During this time, the brain refines its connections significantly. Between 34 weeks after conception and 2 years of age, the brain develops most synaptically and expands dramatically. Synaptic density reaches adult levels by the time a child is in preschool. Some areas of the brain, such as the frontal lobes, which govern higher cognitive skills, continue to myelinate well into adolescence, but other regions of the brain, which control more basic functions, myelinate sooner (Toga *et al*., 2006) [17]. Although distinct sections of the brain's gray matter (which houses nerve cells' bodies) achieve asymptote by the ages of 7 to 11, it is believed that the growth of the white matter (which represents axonal nerve tracts) continues past the age of 20. According to studies, the development of particular cognitive abilities like language, reading, and memory during childhood is linked to the maturity of particular brain regions. The frontal lobes' development, which is thought to be responsible for higher cognitive processes like planning, sequencing, and self-regulation, appears to take place in growth spurts during the first two years of life, then again between the ages of 7 and 9 and again around the age of 15 (Bryan *et al*., 2004) [2]. The basal ganglia, amygdala, and hippocampus are a few of the subcortical structures whose development lasts until late adolescence and which are essential in mediating various higher cognitive skills, such as memory, executive processes, and emotion. Since the first two years of life are a time of rapid brain development (the brain reaches 80% of its adult weight by the age of two), this time frame may be particularly vulnerable to dietary deficits. Research shows that structural rearrangement, brain and cognitive maturation, and—in particular—significant changes in the pre-frontal cortex occur throughout puberty, making adolescence an equally important and delicate developmental stage (Blakemore *et al*., 2010) [1].

Effect of Zinc on Brain Development

Zinc is a crucial micronutrient that may be obtained as a dietary supplement as well as naturally occurring in some foods. It participates in a variety of cellular metabolic processes and is necessary for the catalytic activity of over 100 enzymes (1). It is also essential for immune system function (2) and cell division (3). In the course of pregnancy, childhood, and adolescence, it is said to assist the fetus' natural growth and development (4). Due to the high demand for zinc by developing fetuses, pregnant women are more prone to acquire zinc deficiencies and have negative health effects as a result.

Risk of Zinc deficiency: Zinc shortage often results from insufficient zinc intake or absorption, increased zinc losses from the body, and increased zinc demand. Pregnant ladies are aware of all these issues. Women who are pregnant are more vulnerable to zinc deficiency, especially in the second and third trimesters. Increased blood volume, poor bio-absorption, and consumption of zinc are the causes of this. It is also connected to anemia brought on by iron deficiency.

(a) Effect of zinc on pre natal stage: Zinc is a crucial element for the neurodevelopment of a fetus because it is essential for enzymatic activity, involved in cell replication in brain growth, zinc finger protein in brain structure, and involved in neuro transmission. It is also involved in many metabolic processes like hormone transport, receptor binding, and the production of neuro transmitter precursor.

(b) Effect of zinc on post natal outcomes: Due to its importance in the transfer of several immunologic components and vitamin A, maternal zinc insufficiency causes problems that are not just restricted to the fetal life but also arise in the postnatal period. Perinatal zinc shortage may have a negative impact on the healthy growth of several tissues and organ systems in the fetus by impairing the development of natural immunity and decreasing the acquisition of antibodies from the mother. In addition to stifling immunological responses, it has also been linked to decreased spleen and thymus size, reduced lymphocyte mitogenic responses, plaque-forming activities, and lower concentrations of immunoglobulin M and immunoglobulin A. Zinc is needed as a cofactor for the transport of immunoglobulins over the placental barrier, hence zinc shortage during pregnancy may reduce the fetus's ability to acquire antibodies in utero. Therefore, a zinc shortage may contribute to lower immunity, decreased vaccination effectiveness, and poorer disease resistance in fetuses.

Effect of Zinc on Learning and Behaviour Abilities

Animals whose zinc intake was restricted during pregnancy or particular developmental stages were used to study zinc deficiency. Zinc deficiency throughout the prenatal and neonatal periods has been studied in rats. Animals with significant zinc deficiency early in embryonic development were more likely to miscarry and have malformed babies. Animals with zinc shortage who were refed and tested as adults had trouble learning mazes, especially when shock was employed as the teaching method. This was true even when the zinc deficiency occurred after the time of organogenesis but during early development. Their hostility, poor recall, and trouble avoiding the shock were all signs of elevated

emotionality in their response. Consequently, zinc shortage early in life appeared to have long-lasting impacts on the animals' reactions to stress, which hindered performance in learning scenarios.

Effect of Zinc on Biochemical Parameters

The effects of Zn shortage on a few hematological parameters in rats were studied, and it was discovered that both male and female rats significantly decreased in Hb, total erythrocyte count, and packed cell volume. A decrease in hemoglobin content might be caused by a faster rate of erythrocyte disruption or a slower rate of erythrocyte synthesis. The lower cellular count in the blood of Zn-deficient rats was clearly responsible for the decline in packed cell volume. According to research, dietary Zn shortage in rats enhanced the osmotic fragility of their erythrocytes, and the reduced erythrocyte stability was caused by oxidative damage. They discovered that spleen cell counts were decreased with Zn deficiency.

Effect of Iron on Brain Development

Iron insufficiency is one of the most prevalent dietary deficits in both developing and industrialized nations. The frequency is higher than 40% in various regions of the world, including South-East Asia and Sub-Saharan Africa. According to Rioux *et al*. (2011) [16], it is thought that iron interacts with a variety of enzyme systems in the brain, including those that produce energy (cytochrome c oxidase), make dopamine receptors (tyrosine hydroxylase), make myelin (delta-9-desaturase), make fatty acids (delta-9-desaturase), and regulate brain growth (ribonu-cleotide reductase). Children are most at risk for iron deficiency at the following three stages of development: during the fetal/neonatal stage, during infancy and the early toddler years (6–24 months), and after the start of menarche in females. During the first two of these times, brain growth and development is pretty quick, and the third time it is almost finished. This contrast enables researchers to compare how a single nutritional shortage affects a developing brain in comparison to a mature brain. One may anticipate significant neuroanatomic changes in a brain that is still developing due to its complicated participation in cell cycle kinetics and myelination, but one might not expect any structural changes in a brain that is quite mature. Since myelination is nearly complete by the time a person reaches their teen years, iron shortage should not damage it. However, iron deficit in children before the age of three will probably cause significant, potentially permanent abnormalities to the myelin sheath. Furthermore, the most impacted locations can be those that are expanding particularly quickly. Iron shortage during one growth stage, such as prenatal life, may result in quite different neuroanatomic and neurobehavioral abnormalities than iron deficiency during another growth period, such as infancy, since the brain does not develop homogenously, meaning that not all portions mature at the same time. The effects of iron on oxidative phosphorylation and monoamine metabolism have significant implications on neurochemistry and neuro metabolism as well. In both developing and mature brains, an iron deficit may have comparable effects on various chemical and metabolic elements of brain function. As a result, iron deficiency might affect neurotransmitters like dopamine and glutamate at any age.

Effect of Iron on Behaviour Abilities

Infants of moms with iron-deficiency anemia tend to be more irritable. In the other, lower cord blood ferritin and hemoglobin levels at birth were associated with lower levels of alertness and soothability and greater levels of negative emotionality (Wachs *et al*. 2005) [18].

Effect of Iron Biochemical Parameters

The human baby starts accumulating iron early in pregnancy, grows substantially in the third trimester, and keeps doing so up to 30 to 50 years after delivery. Term infants are typically thought to be protected from IDA through the first few months of life, unless maternal iron deficiency is severe, but as iron stores are used up, a sharp decline in serum ferritin occurs and the infant becomes vulnerable to deficiency if the supply of dietary iron is insufficient. Preterm newborns are particularly susceptible to early iron shortage because they have 40–70% less total body iron at birth than do mature infants. According to rat studies, iron builds up in the prenatal and postnatal brain in a comparable fashion. Contrary to the quick turnover of iron in plasma, iron is sequestered once within the brain and has a relatively low turnover rate. Reduced iron concentrations in tissues and biochemical alterations in the blood are consequences of dietary iron insufficiency. According to widespread consensus, IDA refers to a level of dietary iron deficiency that is enough to deplete ferritin reserves and lower iron concentrations in specific tissues, but not enough to cause anemia-level drops in serum hemoglobin. People who have depleted iron reserves and serum hemoglobin levels that are below the 98th percentile of a population with a normally distributed distribution are often categorized as anemic and iron deficient.

Effect of Iodine on Brain Development

Iodine deficiency affects millions of people globally, especially infants and expectant mothers (World Health Organization, 2004) [19]. Food fortification, most frequently the use of iodized salt, has become prevalent due to iodine shortage in the soils of many nations (WHO, 2004) [19]. There has been much research on the relationship between odine and cognitive development. The possibility of "cretinism" in infants as a result of severe iodine deficit during pregnancy is now well accepted (Zimmermann, 2011) [20]. The clinical symptoms of cretinism might include mental retardation, speech and hearing impairment, upper motor neuron and extrapyramidal lesions, depending on the degree of iodine shortage. According to Melse-Boonstra and Jaiswal (2010) [13], the thyroid gland contains 70–80% of the iodine that the body needs to produce thyroid hormones. Triiodothyronine (T_3) and thyroxin (T_4) are two thyroid hormones that are under produced as a result of iodine shortage, which causes hypothyroidism. The differentiation, maturation, migration, myelination, neurotransmission, and synaptic plasticity of neuronal cells, as well as other neurological processes, are all significantly influenced by thyroid hormones (Zimmermann; 2011) [20]. Hypothyroidism also affects neurogenesis and the growth and operation of synapses in the hippocampus in animal models.

Effect of Selenium on Brain Development

Selenium is a vitamin whose significance for brain growth is just now becoming understood. Selenium shortage is observed in geographical areas with low soil selenium levels. Because of the decreased selenium concentration of the food crops and pasture grasses cultivated in these soils, communities that

depend on locally produced food and animal products are at risk for selenium insufficiency. Communities residing in various low-soil-content regions of China have the highest prevalence of selenium deficiency (FAO/WHO, 2004) [19]. Due to the importation of crops and animal products produced in places with high soil content, the rates of selenium insufficiency have decreased in a number of other low soil content locations (such as Finland, New Zealand, and the United Kingdom). Finally, due to their lower body reserves and typically worse antioxidant status, preterm newborns are another demographic that is at a somewhat high risk of selenium insufficiency. Selemium's function in thyroid and iodine metabolism in the brain, as well as its interactions with other micronutrients (such as iron, copper, zinc, and lead) that affect brain development, are significant despite the absence of direct evidence of its impact on human cognitive development. The creation of proteins known as selenoproteins, which are involved in thyroid metabolism, depends on selenium. Selenium insufficiency can therefore cause hypothyroidism and cretinism, much like iodine deprivation did.

Effect of Copper on Brain Development

A crucial part of the proteins needed for proper brain function is copper. Cu has, however, been linked to the pathophysiology of neurological diseases including Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis. Neuronal degeneration, elevated levels of Cu, Fe, and Zn, and increased amyloid protein deposits are all symptoms of Alzheimer's disease (AD). The amyloid precursor protein gene molecule in Alzheimer's disease features a Cu-binding site and has been associated with the illness's early-onset variants. Two cysteine molecules are converted to cystine and two electrons are created as a result of the binding of Cu2+ to amyloid precursor proteins *in vitro*. Cu_2+ can be reduced with just one electron, thus it's possible that the extra electron is used to create hydroxyl radicals. ROS formation may be aided by the binding of the amyloid protein to Cu and Zn. In yeast lacking SOD, the Cu transport protein Atox1 acts as a Cu-dependent suppressor of oxidative damage. Serum starvation and oxidative stress are protected against in neuronal cell lines that have had the Atox1 gene transfected to raise the endogenous level of Atox1 expression. As a result, Atox1 could protect brain cells from oxidative damage brought on by Cu (Gaetke *et al*., 2003) [5].

The hippocampus, which is linked to neurogenesis and long-term memory storage, is one of the earliest and most severely affected brain regions in AD. Additionally, compared to other brain regions, it is regarded to be more vulnerable to metal disruption. The cortex, which is connected to mental processes like reasoning, emotion, and language, is another area of the brain that experiences impairment in AD as a result of plaque disease. Defective brain areas had a very low copper level, according to research on the human brains of deceased dementia sufferers (Pickart *et al*., 2017) [15]. According to Exley *et al*. (2012) [3], there is a substantial negative link between the amount of copper in old human brains and how severe the amyloid plaques are. It has been postulated that AD is caused by a copper deficit based on research demonstrating a large decrease in copper ion in AD patients compared to controls (Giacoppo *et al*., 2014) [6].

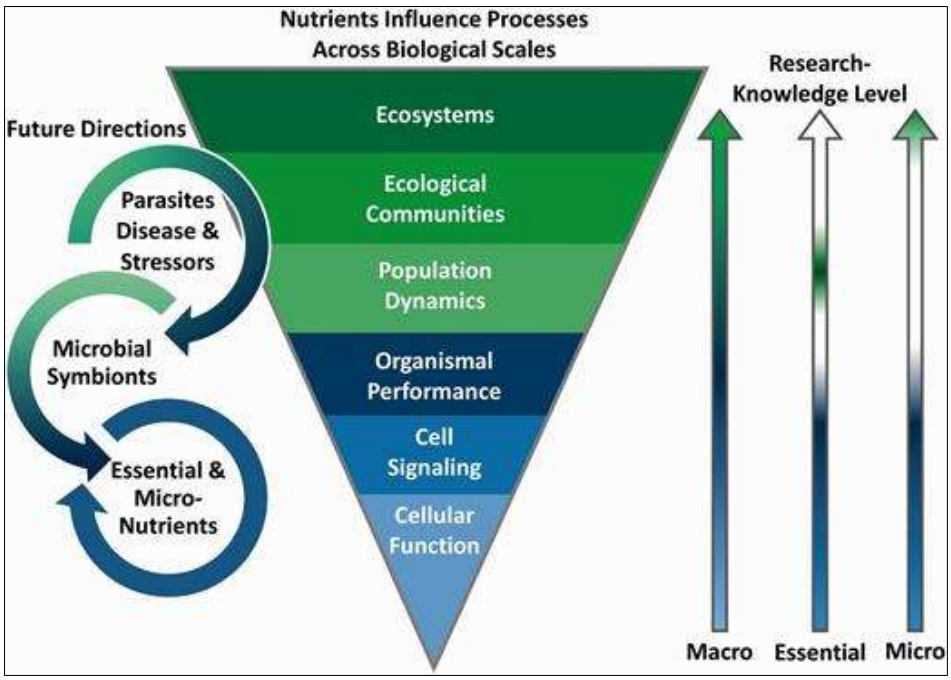

Fig 2: For each of the major classes of nutrients, an illustration of the present level of knowledge on the effects of nutrients across biological scales (vertical arrows and triangular sections) is shown

Conclusion

Micronutrients are vital parts of the human diet and support development, performance, and growth. It is well recognized that the roles and effects of micronutrients can vary during the life cycle and that a proper diet is necessary to ensure these functions and effects. Nevertheless, a number of studies and meta-analyses have found that many micronutrients are not sufficiently given throughout the life cycle. Depending on the significance of the micronutrient that is inadequately given at a particular period of the life cycle, this may or may not have negative health repercussions.

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