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Hidden Hunger – Consequences for Brain Development

Konrad Biesalski

Introduction

Whenever we see a report in the evening news about a massive famine, which killed thousands, then generally for the first time we become aware that there are people on the planet who live in poverty and starvation. It is important, however, that we differentiate between 'hunger' and 'starvation' as these are two very different conditions. Hunger is a two-sided coin. It refers simultaneously to that which is visible and can be subjectively and objectively viewed, and that which is hidden. The visible hunger, undernourishment with very low body weight, is a result of an inadequate energy intake. The affected are more or less wasted as a result of the energy need of the body and subsequent depletion of his own fat stores and muscles.

This less-visible hunger is defined as 'hidden hunger'. Hidden hunger or chronic malnutrition can be defined as a low supply with essential micronutrients e.g. vitamins, minerals etc. Hidden because typical signs and symptoms of severe deficiencies are absent as long as a small amount of the micronutrients is present in the diet. If, at least, the body stores are exhausted typical symptoms may occur which finally but often too late unhide the hidden hunger.

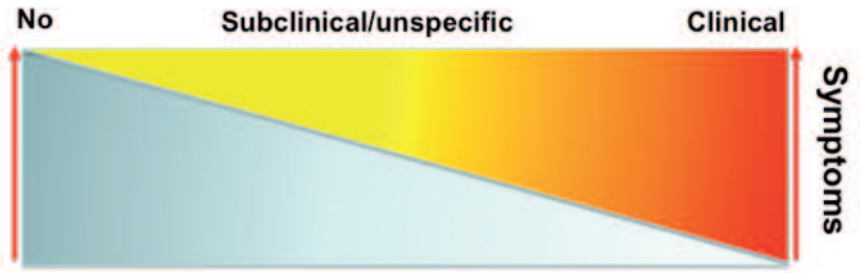

Figure 1.

Figure 1 shows a scheme of hidden hunger. Supply of a micronutrient declining from left top to right bottom. As long as the supply of a micronutrient is not near zero, specific clinical (e.g. scurvy and vitamin C-deficiency, or

night blindness and at least blindness and vitamin A deficiency etc.) signs will not develop. However, long before, the inadequate supply results in more or less unspecific symptoms such as increased risk for infectious diseases (vitamin A and iron-inadequacy) or chronic diarrhea (zinc deficiency) occur.

Currently, three billion people are affected by hidden hunger. In particular iron, iodine, zinc, vitamin A and D are the major candidates of hidden hunger. Year after year it is hidden hunger, not only the physical torture of starvation, which is responsible for the deaths of millions of men and women, but the majority are children. Chronically malnourished women and children, most of all, are the ones who face the highest risk of suffering illness or death before having taken their first real steps in life. This is the real tragedy! Hidden hunger remains invisible over a more or less long period of life.

Box 1. Adverse effects of malnutrition among children [1].

- 186 million children under the age of five (30% of all children in this age group) suffer from stunting.
- 115 million children under the age of five suffer from wasting.
- 20 million children suffer severe and life-threatening malnutrition.
- 3.9 million children (35% of all fatalities) die from a lack of breast milk (or from breast milk with not enough nutrients), as well as from a micronutrient deficiency, most especially vitamin A, iron, iodine and zinc.
- In many countries, a child's diet after weaning (generally six months after birth) is not sufficient to provide it with the quality it needs for the first two years of its life.

Even in cases with adequate energy supply the missing micronutrients cause physical and cognitive impairment of the growing child. From the beginning of their life these children are captured in a vicious cycle of malnutrition and poverty. Poor physical strength and low educational level are the basis to remain in poverty and malnutrition.

Poverty and chronic malnutrition are inseparable, and yet the connection is very often overlooked. This combination dictates the daily activities of some 2.5 billion people. Despite numerous attempts to remedy this predicament and even more cries for change, there have hardly been any improve-

ments during the past 25 years. In fact, the growth-centered globalized economy has led to even greater poverty levels, whereby the poor remain in the background. They may move temporarily to the forefront whenever a region is struck by famine, but then they inevitably disappear again into the shadows of the abyss and the hidden hunger remains.

The phenotype of hidden hunger

To understand the phenotype of hidden hunger, undernutrition and malnutrition need to be discriminated (Box 2).

Unternutrition is, according to the FAO, an intake of calories expressed as daily Dietary Energy Consumption (DEC)[2] which is less than the Dietary Energy Requirement (DER) (Cafiero & Gennari 2011). Using this formula, the number of undernourished or hungry persons in any population can be calculated. To determine the DEC, factors such as gender and light manual labor are taken into the equation, as well as data regarding the average daily requirements from the Food Balance Sheets (see below). The percentage of undernourished individuals is projected based on the averages values over a three-year period. Hence the term 'undernourishment' is expressed strictly in terms of quantity, whereby the undernourished are understood as having an insufficient energy intake in relation to their physical workload. As a result, the phenotype undernourished individual is underweight and 'under-productive'.

Malnutrition in contrast is a qualitative description, i.e. those persons affected by it have a deficiency of one or more nutritional components without necessarily consuming too few calories. If the average caloric intake of the population is calculated as being sufficient, no measures are undertaken to determine what percentage of that population is malnourished. By definition, a person who is undernourished is malnourished. Yet the opposite is not true, namely a person need not be undernourished to be malnourished and may even be overweight. The phenotypical malnourished individual is recognizable either due to symptoms arising from a specific nutritional deficiency (e.g. iron deficiency anemia) or because he or she often falls ill or shows signs of a developmental disorder (stunting).

The phenotype of undernutrition is wasting, the phenotype of malnutrition (hidden hunger) is stunting (Box 3).

Wasting (W/H › -2 SD) is the most serious form of undernourishment and it effects 10% of children under age five (i.e. 55 million children). 3.5% of children younger than five (i.e. 19 million children) suffer from a severe case of wasting (› -3.5 SD). Wasting is a visible signal of ongoing and acute undernourishment, depending upon the original bodyweight of the individual and it is the result of an insufficient diet (in both the qualitative and quantitative sense) or a serious illness.

Stunting (H/A ‹ -2 SD) Children who suffer from stunting deviate from the average height of children in the same age group and population group by more than two SD. Unlike wasting, stunting is the same as being underweight since it is the result of chronic malnutrition. Those affected suffer from growth disorders and mental handicaps.

Restricted growth, defined as stunting, is a consequence of malnutrition during pregnancy and frequent infectious diseases and malnutrition during early childhood. The latter is a consequence of an impaired immune system due to malnutrition. Infections further deplete micronutrient body stores and promote malnutrition, and subsequently malnutrition negatively affects the immune system and promotes infections. Beside the above-mentioned factors, inadequate provision of care and living conditions may also have an impact on the development of stunting. Stunting however is not an isolated sign of growth retardation, but also a biomarker for a more or less impaired development of the brain.

The major reason for hidden hunger worldwide is poverty and poor education. Therefore hidden hunger occurs in developing and in developed countries, but to a different amount and magnitude (Table 1, 2).

It is evident that the prevalence of hidden hunger is highest in developing countries, but also occurs in more developed regions. The fact that malnutrition does not only cause an impairment of childhood development, but increases mortality in children below the age of five is inacceptable. The leading causes of childhood death are vitamin A- and zinc-deficiency.

Data depicted in table 3 show that deficiency of iron, iodine, vitamin A and zinc in pregnant women and children below the age of five, is not only present in developing countries, but also occurs in Europe to an extent, which is not marginal, with respect to childhood development. In some cases the prevalence is similar between low- and high-income countries. However, the severity of the deficiency consequences might be different but not the reason.

Table 1. Prevalence of the three major micronutrient deficiencies by WHO region [3].

	Anemia[a] (total population)		Insufficient iodine intake[b] (total population)		Vitamin A deficiency[c] (preschool children)	
	n (millions)	% of total	n (millions)	% of total	n (millions)	% of total
WHO region						
Africa	244	46	260	43	53	49
Americas	141	19	75	10	16	20
South-East Asia	779	57	624	40	127	69
Europe	84	10	436	57	no data available	
Eastern Mediterranean	184	45	229	54	16	22
Western Pacific	598	38	365	24	42	27
Total	2,030	37	1,989	35	254	42

[a]Based on the proportion of the population with hemoglobin concentrations below established cutoff levels.
[b]Based on the proportion of the population with urinary iodine ‹ 100 µg/l.
[c]Based on the proportion oft he population with clinical eye signs and/or serum retinol 0.70 µmol/l.

Table 2. Global deaths and DALYs in children ‹ 5 years of age attributed to micronutrient deficiencies [3].

	Deaths	% of deaths in children ‹ 5 years	Disease burden (1,000 DALYs)	% of DALYs in children ‹ 5 years
Vitamin A deficiency	667,771	6.5	22,668	5.3
Zinc deficiency	453,207	4.4	16,342	3.8
Iron deficiency	20,854	0.2	2,156	0.5
Iodine deficiency	3,619	0.03	2,614	0.6

Table 3. Hidden hunger in children ‹ 5 and pregnant women in developed countries [4]. Prevalence of vitamin A deficiency (1995-2005), iodine deficiency (2013), inadequate zinc intake (2005), and iron deficiency anemia (2011). Data are % (95 % CI). UIC = urine iodine concentration.

	Vitamin A deficiency			
	Children < 5 years		Pregnant women	
	Night blindness	Serum retinol < 0.70 µmol/L	Night blindness	Serum retinol < 0.70 µmol/L
Global	0.9 % (0.1 – 1.8)	33.3 % 29.4 – 37.1)	7.8 % (6.5 – 9.1)	15.3 % (6.0 – 24.6)
Africa	2.1 % (1.0 – 3.1)	41.6 % (34.4 – 44.9)	9.4 % (8.1 – 10.7)	14.3 % (9.7 – 19.0)
Americas and the Caribbean	0.6 % (0.0 – 1.3)	15.6 % (6.6 – 24.5)	4.4 % (2.7 – 6.2)	2.0 % (0.4 – 3.6)
Asia	0.5 % (0.0 – 1.3)	33.5 % (30.7 – 36.3)	7.8 % (6.6 – 9.0	18.4 % (5.4 – 31.4)
Europe	0.7 % (0.0 – 1.5)	14.9 % (0.1 – 29.7)	2.9 % (1.1 – 4.6)	2.2 % (0.0 – 4.3)
Oceania	0.5 % (0.1 – 1.0)	12.6 % (6.0 – 19.2)	9.2 % (0.3 – 18.2)	1.4 % (0.0 – 4.0)

	Iodine deficiency (UIC < 100 µg/L)	Zinc deficiency (weighted average of country means)	Iron deficiency anaemia (haemoglobin < 110 g/L)	
			Children < 5 years	Pregnant women
Global	0.9 % (0.1 – 1.8)	33.3 % 29.4 – 37.1)	7.8 % (6.5 – 9.1)	15.3 % (6.0 – 24.6)
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Malnutrition, the escort of poverty

The association between childhood poverty and negative developmental outcome is long established. One determinant of poor development is malnutrition. The reason for malnutrition is low household expenses to buy different food and to achieve adequate diet diversity.

Figure 2 shows the major reasons for hidden hunger, and the relation between income and diet diversity related to the risk of micronutrient deficiencies in low-income countries [5].

According to Deaton and Subramanian [6] the poorest people consume on average slightly less than 1.400 kcal/day. This amount of energy does not even cover the daily need. But also an increase of energy with increasing amount of starchy food is far from being adequate with respect to sufficient nutrition. The extremely poor (less than 1US$ income) spend nearly all money to buy starchy food. If the diet is composed mainly of starchy food, the risk of micronutrient deficiency is high. Starchy food creates satiety but is poor in nearly all micronutrients. The higher the diet diversity the higher the micronutrient content, and the lower the risk for micronutrient deficiencies. From the figure it is also easy to understand why even small changes in food prices of starchy food will lead to increased micronutrient deficiencies. The poor become very poor and the very poor join the group of the extremely poor. The critical role of starchy food is underlined by a recent calculation of the FAO (FAO, 2013)[7]. The report did not find a strong correlation between undernourishment and stunting, or average dietary energy supply. But the relation between the amount of starchy food (cereals, roots and tubers) in the daily diet and stunting was strong. If the daily amount exceeds 65% (total energy) within a household the number

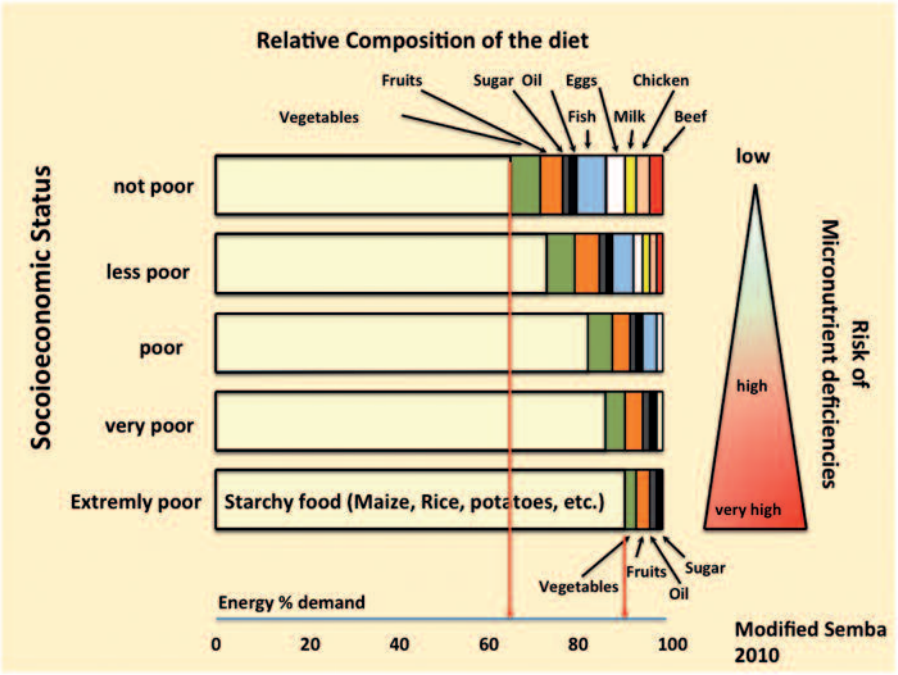

Figure 2.

of children stunted is greater than 40% in a country. Based on the data that the daily amount of starchy food in the diet has not really changed within the last twenty years (30% in developed regions, 60% and more in developing countries), the number of undernourished children may decrease due to increased availability of starchy food, but the number of malnourished might be unchanged.

The major risk groups affected by malnutrition are women and children. Consequently malnutrition at the time point of conception is not a rare case and will trigger a couple of events during the first 1000 days of life of a child. The focus of the following discussion on micronutrients and brain development will be therefore restricted to the first 1000 days of life, although micronutrients might exert effects on health and cognition later on in life.

The 1000-day window – a development window which might be irreversibly closed

During the first 1000 days of human life, from conception until the second year of life, the most important developmental steps occur. The nutri-

tion status of the mother at the time point of conception is a critical condition with respect to embryonic development.

Intrauterine growth retardation results in low birth weight of the newborn. Major determinants of low birth weight, in particular in developing countries, are poor nutritional status of the mother and subsequent low nutrient flow to the developing child. Newborns with low birth weight (<2,500g) are four times more likely to die during their first 28 days of life than those weighing 2,500-2,999g, and 10 times more likely to die than newborns weighing 3,000-3,499g [8]. Low birth weight is, however, the phenotype of intrauterine stunting and consequently also a visible marker for a potentially impaired brain development. Indeed, it was documented that the effect of stunting on short-term memory was equivalent to the difference in short-term memory between children in US families that had experienced poverty for 13 years and children in families with incomes at least three times the poverty levels [9]. Malnutrition is a frequent companion of poverty not only in developing countries, and has a strong impact on brain development.

Brain development and poverty – fateful relationship

The human brain develops in different steps during embryogenesis. Interneuron connections develop during week 8 to 16 within the so-called cortical plate and are replaced by cortical neurons from week 24 until the perinatal period. The brain growth spurt begins in the last trimester of pregnancy and continues in the first two years after birth. During this time the majority of dendritic growth, synaptogenesis and glial cell proliferation occurs [10,11]. During the first 2 years of life (by the age of 2 the brain has 80%-90% of adults weight), this period is highly sensitive to deficiencies of micronutrients [12,13].

The structure of the brain at any time is a product of interactions between genetic, epigenetic and environmental factors [14]. Environmental factors include outside events and the internal physiological milieu. Consequently poor nutrition or stress will have an impact on brain structure and ultimately on its function. The connection between stress and poor nutrition is poverty. Developmental cognitive neuroscience dealing with poverty and social gradients is a new field of research, which emerged recently. It has recently been shown that pregnancy and growing up in a low socio-economic status (SES) will have neural and cognitive consequences [15,16].

Children living in poverty have poorer cognitive outcome and school performance. Poor SES is related to reduced attention, literacy and numeracy function which, beside other factors, may explain the poor educational level of children living in poverty [17]. Language and memory functions are related

to brain regions sensitive to environmental and nutritional influences. Research in both animals and humans suggests that the experience of stress has important negative effects on the hippocampus and the amygdala which are highly susceptible during the late fetal and early neonatal period.

The amygdala and hippocampus serve emotion, language, and memory, functions that change markedly between age 4 and 18 years [14]. Amygdala and hippocampus volumes increase with age. Both are involved in stress regulation and emotion processing and are sensitive against environmental stimuli including nutrition. Different studies report lower hippocampal volume in children and adolescents (age 5-17) from lower-income backgrounds compared to the same age group from higher SES [18,19,20].

Poor nutrition as a result of poor income is not the only reason for developmental changes of the brain. Poverty is strongly associated with other factors with an impact on brain development, such as unsupportive parenting, poor education, lack of caregiver education and high level of stressful events. In particular, the income-to-need ratio, for example, to ensure daily nutrition, among others, might become a stressful event which influences brain development [21]. Income-to-need ratio – but not parental education – was positively associated with hippocampal size [18,19]. Stressors more directly related to income, such as limited access to material resources, e.g. variety of food, may have greater influence on hippocampal size than parental education related to cognitive stimulation and parenting style.

A study with healthy children in France showed a positive correlation between SES reading and verbal abilities and literacy [20]. The neural correlate was a significant correlation of SES and local gray matter volumes of bilateral hippocampi. Similar results were obtained from a study of US-American households, documenting a significant positive relationship between income and hippocampus gray matter volume. The authors suggest that differences in the hippocampus, perhaps due to stress tied to growing up in poverty, might partially explain differences in long-term memory, learning, control of neuroendocrine function, and modulation of emotional behavior. Lower family income may cause limited access to material resources, including food, which may be more important for predicting hippocampal size [22].

Two independent studies which might have used part of the same group of children in Germany (Brandenburg) documented an impact of SES on physical and cognitive outcome. The first study [23] investigated children at admission into primary school (aged 6 years in the year 2000) and documented an impairment of literacy in 18.2% of the children from low SES compared to 8.2% mean SES and 4.3% in high SES, and a impairment of cognitive development of 13.2% vs 2.8% vs. 0.9%.

In another study, anthropometric data from children living in Brandenburg on the effect of unemployment on childhood development was investigated [24].

Data from 253,050 preschool children during 1994-2006 were used and the authors stated that,

> *After an initial substantial height increase of school starters in the Eastern German Land of Brandenburg between the re-unification of 1990 and 1995, the upward trend stopped suddenly and even developed into a downturn in children's heights between 1997 and 2000. Since 2000, heights have been stagnating at a low level. This is all the more remarkable, as heights have never declined over longer time spans in Eastern German Laender since 1880 – except for the most recent period 1997-2006.*

They further conclude:

> *The interaction terms of unemployment and additional children are remarkably large. Above, it was already shown that households with four and more children fall behind smaller households with regard to children's height, the former's children being significantly shorter (-1.8 cm). The unemployment variable subtracts another height coefficient of -0.3 cm, in addition to the 'normal' sibling effect! In addition, if the parents are unemployed, the detriment is even larger.*

The height difference is around 1SD from the 95% percentile of children within that area, so it cannot be defined as stunting but it must be taken seriously. Together with the data from the other Brandenburg study showing a massive impact of SES on cognitive development in one of the richest countries of the world, the data are alarming because this has consequences for the later success of the children in terms of better education and income to escape from poverty. Accordingly, it was very recently reported in an analysis of ten European countries that economic conditions at the time of birth significantly influence cognitive function later on in life [25]. The authors argue that birth during a time of recession may lead to a low quality and/or quantity of food which impacts development during that time, with consequences later on in life.

Poor nutrition is not only documented in low-income countries but also in families living in poverty in high-income countries [26]. Diet quality is not only affected by age, traditions or personal preferences but also by education, living conditions and income, important indices of SES and social class. If the income-to-need ratio is not sufficient to ensure an adequate food pattern, either other needs (education, medicine) are reduced or the diet becomes poorer and poorer with respect to quality. If food costs rise, food selection narrows to those items providing the most energy at the lowest cost. When these conditions persist, essential nutrients disappear from the diet and

malnutrition develops [27,28]. Indeed, a recent study on the effect of poverty on children's living conditions showed that, beside a lack of cognitive stimulation, food insecurity also has a strong association with income [29]. There is clear evidence that the SES has a strong impact on dietary quality because diet costs are positively related to food with a higher quality [30].

The individual driving force of food selection is to reduce hunger with an appropriate quantity of food! Food quality is then the second choice. Indeed, when indicators of well being in children living in poverty were compared in the US [31], the most obvious difference was related to "Experienced hunger (food insecurity) at least once in past year". 15.9% of poor children compared to 1.6% of non poor, a nearly 10-fold difference, followed by child abuse and neglect 6.8-fold, lead poisoning 3.5-fold and violent crimes, days of hospital stays, stunting, grade repetition or high school drop out all 2-fold.

Poverty and low income are often associated with poor dietary quality and, consequently, more or less expressed malnutrition. Although a lot of other factors (parental care, education) are involved, the impact of inadequate supply with essential nutrients on physical and in particular brain development should not be underestimated.

Micronutrients and brain development

Regarding couple of micronutrients we have scientific evidence that they are critically involved in pre- and postnatal brain development. In particular iron, iodine, zinc, folate, vitamin A and D. Micronutrients, which are the major missing sources isolated or in combination in the diet of one third of the world population. Further micronutrients, protein and energy and n-3 fatty acids may also have an impact on brain development.

Table 4 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 effect on brain function depends on the severity of the micronutrient deficiency. In many cases deficiencies do not exist in an isolated form. Other micronutrients may also be involved, depending on the food pattern, and protein-energy malnutrition might be also present. The latter has also a negative impact on brain development [32], but will not be discussed further in this article.

Although further vitamins are discussed to play a role in brain development, studies investigating the effect within the 1000-day window are not available. n-3 fatty acids, derived mainly from fat fish. Studies (n=6) investigating the effect of fish consumption during pregnancy on cognitive outcome showed that higher intakes of fish in pregnant women are linked to higher scores on tests of cognitive function in their children at ages between

Table 4. Impact of selected nutrients on brain development.

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

18 month and 14 years [33]. n-3 fatty acids are not further discussed in this review, because they cannot really be attributed to hidden hunger.

Iron

Anemia due to inadequate iron supply with food is the most common single nutrient deficiency in the world. Two billion people are affected, including approximately 50% pregnant women and children. Iron is delivered and accumulates during the last trimester in a significant quantity and forms around 80% of the newborn's iron store. Inadequate supply during this time places the newborn at risk for iron deficiency anemia. In particular, infants born premature have a high risk of iron inadequacy due to the shortened period of accumulation. Even mild iron deficiency in the mother reduces the accumulation of iron in the fetus, resulting in neonatal iron deficiency. The majority of iron is used for erythropoiesis (red blood cell production) of the newborn. As a consequence, the developing brain of the newborn is at risk for iron deficiency. The most affected part of the brain seems to be the hippocampus. The

human hippocampus is highly susceptible to iron deficiency during the late fetal and early neonatal period. In addition, poorer myelination has been described. Poorer myelination means that the speed of neural transmission is reduced, resulting in minor responses to stimuli of the auditory and visual brain areas [34]. Children (aged 9 to 15 month) from iron deficient mothers, or with iron deficiency during the first years of life, show a delayed electrophysiological response to recognition memory stimuli associated with delayed hippocampal function (established as impaired attention and recognition memory), compared to children with sufficient iron supply [35]. Indeed, it has been shown that iron deficiency results in long term altered gene expression of genes that are critical for hippocampal differentiation and plasticity [36]. This might question a complete recovery under iron supplementation.

A review discussing 14 different studies found associations between iron deficiency anemia and poor cognitive and motor development and behavioral problems in all studies. Longitudinal studies consistently indicate that children anemic in infancy continue to have poorer cognition, school achievement, and more behavior problems into middle childhood [37].

Zinc

Severe zinc deficiency is rare but moderate deficiency or inadequate supply affects up to 40% of the world population [38]. Diets low in animal-derived food (best source of zinc) or high in starchy food (low bioavailability of zinc) promote deficiency. Indeed, zinc deficiency during pregnancy as a consequence of a diet high in starchy food with high phytate (lowers bioavailability of zinc and iron) has been reported to be associated with a lower score on the psychomotor index of infants[39]. Diarrhea, frequently occurring during zinc deficiency and a major disease in children in developing countries, impairs zinc uptake and subsequently accelerates zinc deficiency and further micronutrient deficiencies. Children with a zinc deficiency often suffer from uncontrollable diarrhea, pneumonia and increased susceptibility to malaria. Even a moderate zinc deficiency is enough to promote infection, especially in the intestines. Diarrhea inhibits the proper absorption of micronutrients, which further exacerbates the situation faced by these children.

Zinc is one of the major micronutrients that are important during rapid growth, which places infants during their first years of life at risk for zinc deficiency. The impact of zinc deficiency on brain structure coincides with the period of rapid brain development, which occurs mainly during the first two years of life. Zinc is indeed a vital nutrient for the brain with important impact on functional and structural roles. This includes more than

200 enzymes involved in protein, DNA and RNA synthesis, which need zinc as a cofactor. In synaptic vesicles (important for signal transmission) of the hippocampal neurons zinc is found in high concentrations [40].

Different studies with zinc supplementation during pregnancy revealed controversial results on cognitive development. Zinc supplementation alone may unbalance the availability of other nutrients, or zinc deficiency may not occur alone. Indeed, it has been documented that a combination of zinc and iron showed an improvement in cognition [41]. In this double-blind trial, 221 infants were randomly assigned to 1 of 5 treatment conditions: iron (20 mg), zinc (20 mg), iron+zinc, MVM (16 vitamins and minerals, including iron and zinc), or riboflavin weekly from 6 to 12 months. Iron and zinc administered together and with other micronutrients had a beneficial effect on infant motor development. Iron and zinc administered individually and in combination had a beneficial effect on orientation-engagement. From animal experiments there is good evidence that zinc deficiency affects cognitive development (increased emotional reactions, impaired memory and learning capacity). Experiments with zinc-deficient rats compared to zinc-sufficient fed rats showed changes in hippocampal neuronal morphology and, as a consequence, impairment of memory and learning behavior [42]. Similar observations regarding memory have been made in newborns 6 month of age of zinc-deficient mothers [43].

Another important facet of zinc can be noted during early childhood development. Stunting is an early sign of zinc deficiency in a child's first two years. For this reason, zinc deficiency alone is believed to be a cause for developmental disorders which occur during early childhood [44]. A meta-analysis of 36 studies, which examined the effects of zinc supplements on stunting among children under the age of five, showed that zinc did indeed have a positive effect on promoting growth [45].

Iodine

WHO considers iodine deficiency to be "the single most important preventable cause of brain damage" worldwide. Approximately one third of the world population is estimated to have insufficient iodine intake, in particular in Southeast Asia and Europe [46]. 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 of iodine during pregnancy if optimal intake is maintained. In iodine-deficient regions, however, potentially inadequate iodine stores are rapidly depleted during pregnancy, placing the fetus at risk for developmental impairment, especially of the brain.

Severe iodine deficiency during pregnancy may cause "cretinism", which may include mental retardation as well as speech and hearing impairment. In particular, the impaired cochlear (inner ear) development results in congenital deafness, which is a severe burden in particular in developing countries with missing clinical care and special education to develop the ability to communicate. Children with deafness and vitamin A deficiency, which has resulted in blindness, are the most pitiful sights of hidden hunger.

Iodine deficiency causes hypothyroxinemia (low levels of the hormone thyroxin) in the fetal brain. Within the brain thyroid hormones regulate metabolic rate, myelination and play a special role in glucose transport to astrocytes. Astrocytes are important for energy and nutrient supply to neuronal cells. The fetal brain may become irreversibly damaged due to intrauterine iodine deficiency. Very recently it was documented that maternal mild iodine deficiency in rats causes a delay of the development of the hippocampal nerve fibers (axons)[47].

The effects of mild to moderate iodine deficiency on fetal brain development, however, are less clear. Observational studies from different countries in Europe and USA document a significant association between mild maternal iodine deficiency and cognitive impairment in children. Depending on the severity and onset of iodine deficiency during pregnancy, the clinical signs are more or less expressed. In particular, the severity of cognitive impairment seems to be associated with the degree of iodine deficiency [48]. In early childhood iodine deficiency impairs cognition, but in contrast to fetal iodine deficiency there is evidence for improvement with iodine treatment. Children from iodine-deficient areas had more cognitive impairments compared with children from areas with sufficient iodine [49]. Several European studies showed that isolated iodine deficiency during pregnancy is associated with impaired cognitive development in children (reviewed in [51]).

In a recent observational trial in the UK, the effect of an inadequate iodine status in 14,551 pregnant women on the cognitive outcome of their children (13,988) was evaluated. The data 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 8 years, and reading accuracy, comprehension, and reading score at age 9 years. The authors have shown that the risk of suboptimum cognitive scores in children is not confined to mothers with very low iodine status (i.e. <50 g/g), but that iodine-to-creatinine ratios of 50-150 g/g (which would suggest a more mild-to-moderate deficiency) are also associated with heightened risk [50].

Based on different intervention studies at different ages in children, it is argued that the developmental effects of iodine deficiency during early gestation are irreversible with later iodine repletion [39]. Supplementation of pregnant women, however, showed a clear benefit on the 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 3 months to 3 years) could be clearly documented in three out of four studies [51].

In contrast, supplementation after birth has no clear impact on cognitive development (reviewed in [52]). This underlines the importance of women's adequate nutrition in particular at the onset and during pregnancy [53,54]. In addition, it has to be considered that the newborn depends on iodine from breast milk during lactation. In areas with inadequate iodine supply, breast milk iodine concentration is not sufficient to meet the needs of the infant, even when their mothers were supplemented with 150ug daily iodine during the first 6 post-partum months [55].

Vitamin A

Inadequate vitamin A intake increases the risk of infectious diseases, in particular of the respiratory tract. As a consequence, further micronutrients become shortened due to either higher turnover, or disturbed tissue distribution, or impaired absorption. In addition, vitamin A deficiency is often accompanied by anemia. Both vitamin A and iron share the same sources. Consequently, it is not easy to discriminate the effects. However, based on recent data, Vitamin A seems to have an isolated effect on brain development. In the brain, the levels of retinoic acid (RA), the active metabolite of vitamin A, is relatively high, being highest in the hippocampus [56]. RA is critically involved in induction of neurogenesis (formation of neurons) and control of neuronal patterning (interaction and network between neurons) in the brain. This effect can be explained via strictly controlled formation of RA concentration gradients. Vitamin A deficiency (VAD) may have a negative impact on the plasticity of the hippocampus. Plasticity is required for neural networks to adapt to changes of the environment. This is important for the learning brain and, in the case of VAD, problems of learning and memory may occur [57]. The hippocampus is a region of the brain whose function is critically dependent on plasticity. Reduced hippocampal sizes in VAD rats and reduced learning abilities have been described [58]. According to Barth and co-workers [50], "it might be assumed that VAD seldom occurs in the Western world but recent results have pointed to high levels of RA signaling in hippocampus and it has been shown that human supplementation with RA results in im-

proved learning and memory [59]. This suggests that normal human brain may have suboptimal levels of RA, perhaps of its high demand for the vitamin A". With respect to the impact of VAD during pregnancy and early childhood, VAD may influence hippocampal plasticity and, by the way, learning and memory. But supplementation with vitamin A during pregnancy or even later might help to improve the hippocampal function.

Vitamin D

Vitamin D (VDD) deficiency is a worldwide problem with a couple of health consequences in childhood and in adults. VDD is observed in 60% of Caucasian women and also in women with dark skin, where the rate is estimated to be even higher [60].

It has been frequently described that maternal VDD during pregnancy is associated with adverse health outcome of the offspring, including intrauterine growth restriction and impaired bone mass. Vitamin D deficiency is also related to different cognitive and behavioral dysfunctions e.g. schizophrenia [61]. VDD is more pronounced during wintertime, especially in northern regions, because sunlight is the major trigger for skin vitamin D synthesis. Indeed, schizophrenia is more frequent in high latitudes and birth during wintertime [62].

The fetus depends on the plasma vitamin D levels ($25(OH)D_3$) of the mother because $25(OH)D_3$ passes the placenta and is metabolized to form the active metabolite $1,25(OH)_2D_3$ in the fetal kidney. If the plasma levels of the mother are low, the fetus develops in a state of hypovitaminosis D, which may have consequences such as low bone mineral density in later life and risk of osteoporosis [63]. Infants born to mothers with VDD had significantly lower birth weights and an increased risk of being too small for gestational age compared with infants born to mothers with adequate plasma levels as a sign of vitamin D sufficiency [64]. In case of sufficient medical care, this might be without consequences, but under circumstances of developing countries with missing or poor medical care the lives of these children are in great danger.

Low maternal serum vitamin D levels during pregnancy of 743 Caucasian women in Australia are significant associated with offspring language impairment at 5 and 10 years of age [65]. Beside its well-known actions on bone and the immune system, vitamin D seems also important in the developing brain, controlling gene expression of so-called neurotrophins, which are important for neurogenesis [61].

The developing fetus depends on the vitamin D status of the mother, and if the status is not sufficient supply to the fetus might be inadequate.

Due to the fact that the only natural source of vitamin D are fatty sea fish and sundried mushrooms (present in some traditional diets) dietary supply in women living in poverty is rather poor. The most important source of vitamin D is the skin synthesis of the vitamin from solar irradiation. In cases of high pigmentation and poor sun exposure, either seasonal or due to clothing traditions, the formation of vitamin D becomes critical. The high prevalence of VDD in particular in northern Europe [66], in particular in migrants from the south (up to 70%), should be further investigated with respect to an impact on pregnancy and fetal development.

Conclusion

Nutrition plays an important role for fetal and newborn brain development. If malnutrition reduces optimal metabolic functioning during sensitive periods of cognitive development, that may have lasting negative consequences and may reduce the chance of the child to develop and escape from poverty. Lower physical strength and poorer brain development together are a fateful combination, which leaves the child in a hopeless situation with no chance to escape. Malnutrition during the first 1000 days of life can become a more or less irreversible but preventable burden for the child. Nearly 170 million children are stunted and it can be suggested that stunting is accompanied by impaired brain development.

In developed countries hidden hunger may appear as a single event related either to iron or iodine. Supplementation or advice on how to compose an adequate diet might be helpful. But in less developed countries, or in people living in poverty and food insecurity, a single micronutrient deficiency is a more or less rare case. The total diet composition is poor, resulting in hidden hunger of a couple of micronutrients. With respect to development, the missing micronutrients might act synergistically in a harmful sense on development. Supplementation of one or more micronutrients might be a kind of emergency intervention but is not a sustainable approach.

It should not be overlooked that a real selective deficiency of one micronutrient is a rare case, especially in developing countries. If the supply of a single micronutrient is inadequate and creates clinical symptoms it might not be sufficient to offer a single supplement. Deficiency is a consequence of inadequate dietary patterns containing these micronutrients. For example, the most important source of vitamin A is liver and liver products, followed by egg yolk. Liver, however, is an excellent source of iron in a bioavailable form and of zinc. Other food, e.g. meat or milk, are rather poor sources of vitamin A. Vitamin A also occurs as provitamin A in yellow fruits and vegetables. However, the conversion of the provitamin to the preformed

vitamin is not very efficient and iron and zinc in fruits and vegetables are only present in small amounts. So at the very least it depends on the dietary pattern whether symptoms of VAD or zinc or iron deficiency are present. The clinical signs of vitamin A deficiency or iron deficiency reflect a poor supply of one or both. Depending on the food source, either the signs of VAD or of iron deficiency might be prominent. Substituting only one may overlook the importance of the other.

The tragedy of this hidden malnutrition is the fact that, due to missing assessments and clinical symptoms, no kind of intervention is implemented. In particular, in developed countries it seems hard to believe that there might be a problem. However, different studies show that food insecurity is related to poverty and the risk of malnutrition. A recent study estimated the relation between growth failure at 24 months and adult outcomes [67]. Data from 1338 Guatemalan adults (25-42y) were used who were studied as children (1969-1977). Individuals who were stunted scored worse on tests of reading and intelligence. Stunted individuals were more likely to have lower wages (men), and to live in poor households as adults.

The magnitude of malnutrition on the developmental impairment of children from poor settings is not known, and hard to estimate. But in contrast to problems coming from missing parental care or environmental impacts, adequate nutrition for pregnant women and children might be easier to achieve. However, this requires political will and public awareness. The basic approach is to ensure an adequate nutrition of females in childbearing age to avoid deficiencies during the early phases of pregnancy. This approach involves education and knowledge about the importance of food quality. In cases of selected deficiencies supplementation might be an alternative. However, some studies investigating the effect of supplementation with iron during the 1000-day window failed to show a real benefit on cognitive function [68].

Improved early life nutrition during the first two years of life using a micronutrient-enriched protein supplement showed a positive impact on cognition (reading comprehension and schooling) in adulthood, even after accounting for the effect of education [69]. Exposure to the supplement improved growth rates and reduced the prevalence of stunting at age 3 years compared to non-supplemented children, documenting the impact of adequate food quality on development.

Maturation of the brain regions responsible for higher cognitive functioning continues throughout childhood and adolescence [70]. Neuroimaging research suggests that even relatively brief interventions can lead to measurable differences in brain structure in children, and that this change

is directly related to improvement in cognitive skill [71]. Nevertheless, the earlier adequate nutrition can be ensured, the better is the supply to the brain and the better the adequate development.

Malnutrition must be a top priority of national governments and international organizations. It is not acceptable that, in a globalized world with rapidly growing markets and per capita income, millions of children are born in poverty and will remain there. These children are the human capital of these countries, which should contribute to their economic and intellectual development. However, if these children remain fixed on the hunger carousel, they will again be a kind of starting point for the next generation with the same fate. To stop this carousel we need to unhide the problem of hidden hunger and intervene as early as possible with all players from government, civil and private sectors and the community of all religious parties, with all their available power. We do not only need to feed the world, we need to nourish the world.

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