ILSI India Monograph Series on
Science for Public Health - 1

Nutrition, Lifestyle and Brain Health: A Lifecycle Approach

By

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ILSI INDIA

International Life Sciences Institute India

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International Life Sciences Institute India

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Nutrition, Lifestyle and Brain Health: A Lifecycle Approach

International Life Sciences Institute India

FOREWORD

Nutrition and brain health has been a subject of interest and study for past several decades. Over the years, convincing evidence has emerged to show that certain types of nutrients are needed for proper brain development and brain functions. Nutrition is important at all ages, its quality and quantity may be different.

In recent years evidence is emerging that physical activity also influences the brain health. Malnutrition among children and anaemia among pregnant mothers influence the development of important brain functions. The reports of cognitive decline and stunting among children; increasing incidence of Dementia, Parkinson's and Alzheimer's diseases, among aging population; and prevalence of depression in all ages is a matter of concern.

ILSI-India has set up a Task Force on **Nutrition and Brain Health-from Paediatrics to Geriatrics (NABHI)** to look at the research done on impact of nutrition, lifestyle and physical activity on brain health particularly the above brain related disorders. The Task Force commissioned a study on "Nutrition, Lifestyle and Brain Health -A Lifecycle Approach".

The authors of the study have critically analysed the publications on the subject during the last 10 years, with focus on the key areas such as importance of brain development and health , significance of first 1000 days and role of nutrients in brain development, importance of early life influences on cognitive development, factors affecting brain health through the life course, risk factors for dementia and the strategies to promote brain health. The new and emerging area of gut – brain axis as also role of physical activity including yoga and meditation have been described.

Data generation on various aspects of brain health in Indian population is very important to develop effective strategies. The monograph provides recommendations on areas on which research can be conducted in India. The efforts of authors in preparing such a comprehensive monograph are highly appreciated.

It is hoped that this monograph will be of immense use to students, researchers - both from academia and industry, as well as the government and will help in taking new initiatives for better brain health.

Prof. P. K. Seth
Chairman

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ADHD	Attention Deficit Hyperactivity Disorder
ADLs	Activities of Daily Living
APOE	Apolipoprotein E Gene
ARDSI	Alzheimer's and Related Disorder Society of India
CCPCN	Council on Community Paediatrics and Committee on Nutrition
CDCHU	Centre on the Developing Child at Harvard University
CDCPAA	Center for Disease Control and Prevention and the Alzheimer's Association
CVDs	Cardiovascular Diseases
DASH	Dietary Approaches to Stop Hypertension
DHA	Docosahexaenoic Acid
DNA	Deoxyribonucleic Acid
EDU/WKP	Education Working Paper
EEG	Electroencephalogram
EGCG	Epigallocatechin Gallate
EPA	Eicosapentaenoic Acid
IADL	Instrumental Activities of Daily Living
ID	Iron Deficient
IDA	Iron Deficiency Anaemia
IS	Iron Sufficient
IQ	Intelligence Quotient
IUGR	Intra-Uterine Growth Retardation
LBW	Low Birth Weight
LCPUFA	Long Chain Polyunsaturated Fatty Acid
LMICs	Low- and Middle-Income Countries
MCI	Mild Cognitive Impairment
MDM	Mid-Day Meal
MDS	Maternal Depressive Symptoms
MeDi	Mediterranean Diet
MeSH	Medical Sub Headings
MIND	Mediterranean-DASH Intervention for Neurodegenerative Delay
MMN	Multiple Micronutrient
MMSE	Mini Mental State Examination

MoHFW	Ministry of Health & Family Welfare
MRI	Magnetic Resonance Imaging
NAC	N-acetylcysteine
NIA	National Institute on Aging
NIH	National Institute of Health
PA	Physical Activity
PEM	Protein-Energy Malnutrition
PKU	Phenylketonuria
PUFA	Polyunsaturated Fatty Acid
RCT	Randomised Control Trial
SD	Standard Deviation
SES	Socio-Economic Status
TBI	Traumatic Brain Injury
UNICEF	United Nations International Children's Education Fund
WHO	World Health Organisation

EXECUTIVE SUMMARY

The importance of optimal nutrition, that provides adequate energy and protein to infants, has been emphasized for years. Historically, the emphasis has been on the impact of early nutrition on growth and scant attention has focussed on its implications for brain development. In recent years, there has been a growing body of literature supporting the latter.

Nutrients and growth factors regulate brain development during foetal and early postnatal life. The brain, between 24 and 42 weeks of gestation, is very vulnerable to nutritional insults because of the rapid development of several neurologic processes, including synapse formation and myelination. Conversely, the young brain is remarkably plastic and therefore more amenable to repair after nutrient repletion. The brain's vulnerability to nutritional insults likely outweighs its plasticity. Hence, early nutritional insults result in brain dysfunction not only while there is nutrient deficit, but also after repletion.

Nutrition and Neurodevelopment in Early Life

The first 1000 days from pregnancy to first 2 years of life harbours the greatest opportunity to provide optimal nutrition to ensure normal development of the infant. It is also the time of greatest brain vulnerability to any nutrient deficit. Failure to provide adequate macronutrients or key micronutrients at critical periods in brain development has a lifelong effect on a child. In addition to generalized macronutrient under nutrition, deficiencies of individual nutrients may have a substantial effect on neurodevelopment.

All nutrients are important for brain development; however, some seem to have a significant effect on developing brain circuits during the third trimester and early neonatal period. The effects are regionally distributed within the brain on the basis of which areas are rapidly developing at any given time. These include protein, iron, zinc, selenium, iodine, folate, vitamin A, choline, and long-chain polyunsaturated fatty acids.

Many studies in the past 40 years have evaluated the impact of early life nutrition on development of the central nervous system. These studies have clearly established that reductions in energy and/or essential nutrient supply during the early stages of life have profound effects on somatic growth, and the structural and functional development of the brain. However, the timing and nature of the nutritional insult affects brain development in different ways.

Environmental Influences on Cognitive Development in Childhood

The adult and child brain are not different and consist of the same structures and functions as also the mechanisms. Therefore, cognitive development of infants, children until adolescence requires neural enrichment or new stimuli in their environment to build upon the existing structure, making it more complex through interaction and learning from the environment. Enrichment or stimulation provided through early caring behaviours of caregivers include feeding of adequate good quality nourishing food, verbal interactions and opportunities for learning, and protecting the child from various risks that can obstruct the normal course of development. Genetic and environmental factors including nutrition interact and provide the basis for physical growth, cognitive and socio-emotional development.

Among the multiple early environmental influences, food insecurity and resultant dietary deficiencies, inadequate and poor feeding practices, recurrent and chronic infections, and low levels of infant-caregiver stimulation prevent children from reaching their full potential for growth and development as well as increase the risk of poor health due to reduced immunity. Continuing to live in poverty further exacerbates the consequences leading to a perpetual vicious cycle of loss of intellectual, physical and economical potential especially among infants and young children living in low- and middle-income countries.

Exposure to certain metals like lead, methyl mercury and some pesticides can also severely impact learning abilities and lead to poor brain performance scores in later life. Exposure to these chemicals along with malnutrition may have compounding effects.

Cognitive Decline with Age: Influence of Lifestyle

Decline of cognitive abilities with age occurs in healthy individuals and spreads throughout the lifespan. The mechanisms contributing to normal ageing such as oxidative stress, neuroinflammation and vascular dysfunction are the same as those contributing to the development of neurological diseases. In pathological conditions, these mechanisms get aggravated, caused by different factors like genetic or environmental.

It is not surprising that emerging evidence also suggests that nutritional status is associated with brain health in older ages. Addressing age related decline in neural function is a key to preserving the autonomy and well-being of older people. Age related cognitive decline is by now among the main causes of lost disability-adjusted life years in people over 65 years of age.

Evidence on the role of nutrition in preventing cognitive decline in the elderly is now emerging. In recent years, considerable information has been accumulated on the relationship between gut microbiome and brain function through the gut brain axis. The gut microbiome is highly sensitive to negative external lifestyle aspects, such as diet, sleep deprivation, circadian rhythm disturbance, chronic noise, and sedentary behaviour, which are also considered as important risk factors for the development of Alzheimer's. Evidence for the beneficial effects of dietary fibres and probiotics through management of gut microbes is strongly emerging. There are several published data showing the effects of intestinal dysbiosis, caused by changes in diet, the use of antibiotics, non-steroidal anti-inflammatory drugs as well as the presence of pathogenic microorganisms, on cognitive functions of the brain.

Role of Nutrition and Lifestyle in Maintaining Brain Health

In the Alzheimer's and Related Disorder Society of India (ARDSI) Dementia Report (2020), it is estimated that in the year 2020, 5.3 million people in India above the age of 60 (i.e., one in 27 elderly) had dementia (Kumar et al., 2019). Currently, there is no cure available; therefore, preventive strategies are essential to reduce disease incidence. While non-modifiable risk factors, particularly age and genetic factors, play a major role in the development of dementia, increasing evidence has highlighted the role of modifiable risk factors that exacerbate, or diminish the risk of developing dementia later on in life. Good quality evidence exists identifying the following factors as aggravating risk: depression; type 2 diabetes; smoking; midlife hypertension; mid-life obesity; physical

inactivity; and low educational attainment. Although the evidence is not so strong, factors that may reduce the risk include vegetable intake, Mediterranean diet, and increased cognitive activity. There is also weak evidence suggesting that early-life events, such as the death of a parent, and chronic sleep disturbances in middle age may also exacerbate the risk of developing dementia.

The importance of cardiometabolic risk factors that develop in middle age, such as obesity and hypertension as well as smoking and physical inactivity, suggest that strategies are required that target populations while still in their 40s and 50s, much before they develop dementia. Several countries have now acknowledged the need for preventive strategies targeting dementia and the clear overlap with cardiovascular risk and the risk that diabetes poses suggests that dementia could be added to current chronic disease management programmes located in primary care and to wider programmes of public health.

Of potentially far-reaching consequences is the concept that nutritional conditions in early life may program metabolic functions, leading over time to an increasing imbalance and thus favouring the emergence of diseases states. A macronutrient and micronutrient intake level that has preventive effects against CVD is most likely also to be effective against neurodegenerative disorders. The challenge for nutritionists now is to integrate existing scientific knowledge and further advance applied research on effective ways to attain and maintain optimal brain function throughout the life course.

In India, the role of traditional medicine system and use of herbs have been mentioned in Ayurvedic literature for several pathological conditions and symptomology. Their role in promoting brain health and function has been constantly researched. Some herbs have shown the potential to improve cognition and/or prevent/delay cognitive decline as well as impairment. Although clinical trials are limited, pre-clinical studies show promising benefits. Yoga and meditation as well as the use of herbs and other foods have also been described in Ayurvedic literature and have multiple health benefits for the body and mind. Yoga based health programs are now being conducted to evaluate its efficacy in improving brain health and certain cognitive domains.

The role of nutrition and lifestyle factors in brain development, function and decline is an area which is garnering increasing attention in the recent years. Some pioneering research was carried out in establishing brain growth patterns and influence of genetic and environmental factors on these, several decades ago. However, with the epidemiological and societal transition there is a dire need to examine such influences in light of these changes.

Moreover, the findings are based on studies which are observational in nature and unidentified confounders may bias the results. These studies often lack consistency and detail in description or categorization of lifestyle activities and sometimes in the cognitive outcomes measured as well. Longer duration longitudinal and cohort studies are needed to get a better insight into each of the lifestyle factors that affect cognition.

1. INTRODUCTION

Good brain health enables individuals to comprehend their own abilities and adjust their cognitive, psychological, emotional and behavioural functioning according to various life events faced in order to cope with these situations optimally.

The loss of brain function is not only age-related; genes, gender, early life experiences, socio-economic adversity, chronic disease, and low educational levels may influence it.

1.1. BRAIN HEALTH

According to the National Institute on Aging, National Institute of Health, USA, “Brain health refers to how well a person’s brain functions across several areas”. Aspects of brain health include:

- Cognitive health involving thinking, learning and remembering;
- Motor function such as making and controlling movements, including balance;
- Emotional function of interpreting and responding to emotions (both pleasant and unpleasant); and
- Tactile function like feeling and responding to sensations of touch (pressure, pain and temperature).

Multiple factors affect the health of the brain such as age-related changes in the brain, injuries (stroke or traumatic brain injury), mood disorders (depression), substance abuse (addiction), and diseases (Alzheimer's disease); while some cannot be changed, many lifestyle factors can be modified (NIA, 2020).

The World Health Organization describes brain health as an emerging and growing concept comprising neural development, plasticity, functioning and recovery across the life course (WHO, 2021). A good brain health state enables individuals to comprehend their own abilities and adjust their cognitive, psychological, emotional and behavioural functioning according to various life events in order to cope with the situations optimally. Disruptions in normal brain growth and functioning occur throughout life and present as neurodevelopmental conditions such as epilepsy, brain tumours, intellectual developmental disorders, cerebrovascular disease, headache, autism spectrum disorders, neuro-infections, multiple sclerosis, traumatic injury, Parkinson's disease and neurological disorders resulting from malnutrition (WHO, 2021). Cognitive function includes acquiring information and knowledge and comprises of various aspects like executive function, attention, short-term and long-term memory as well as visuo-spatial skills.

Brain health is a critical factor to ensure the health-related quality of life among the elderly and to preserve their independence (Clare et al., 2017). According to Hendrie et al (2006), "cognitive health is the development and preservation of the multidimensional cognitive structure that allows older people to maintain social connectedness, an ongoing sense of purpose and the abilities to function independently, to permit functional recovery from illness or injury, and to cope with residual functional deficits". The main features include mental abilities as well as acquired skills and the ability to apply these to complete a purposeful task/activity (CDCPAA, 2007).

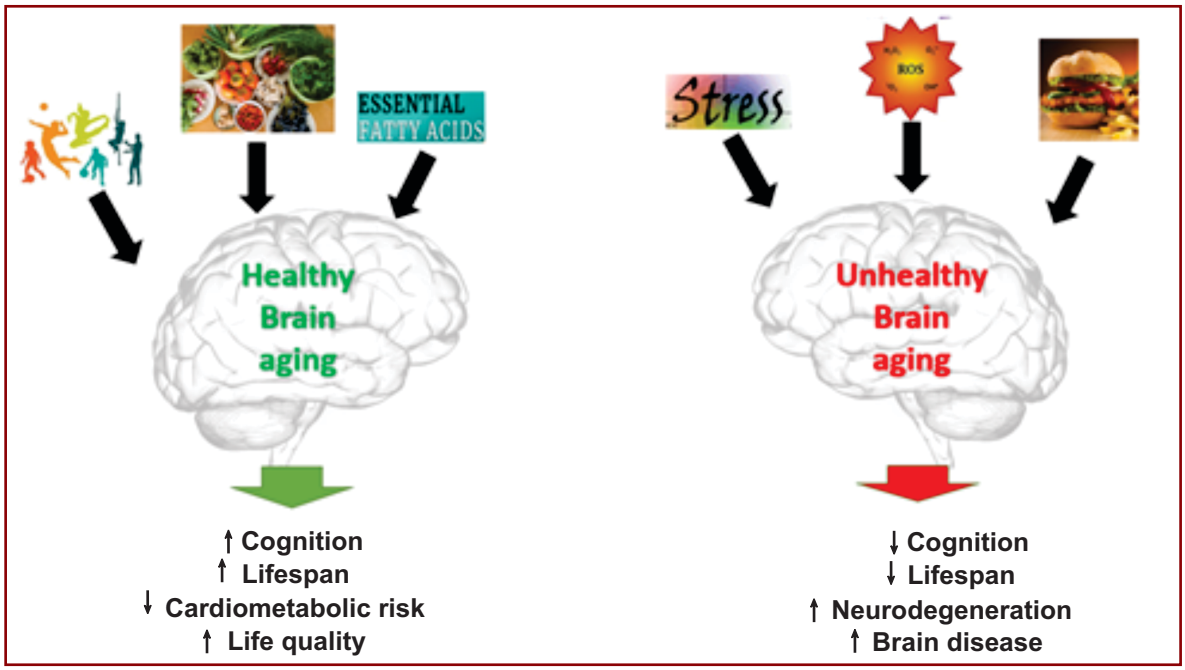

Figure 1: **Brain Dynamics in Healthy and Unhealthy Aging.**

Source: Adapted from Freitas et al., 2017

Figure 1 shows the brain dynamics in healthy and unhealthy ageing. Moderate physical activity, low-calorie diet, and intake of essential fatty acids are amongst the main elements contributing to a healthy brain, where we observe less or no cognitive decline, greater lifespan, reduced cardiovascular and metabolic risks, and overall better quality of life. Conversely, a continuously stressed brain, either due to an unstable environment or due to chemical mediators, e.g., reactive oxygen species (ROS), reactive nitrogen species and other free radicals will suffer from cognitive decline and an increased risk of neurodegeneration and other brain diseases, while affecting the individual's lifespan. Also, high caloric meals and/or typical cafeteria diets are risk factors for the development of several such afflictions (Freitas et al., 2017).

The loss of brain function is not only age-related; gender, genes, chronic disease, early life experiences, socio-economic adversity and low educational levels may influence it (Clare et al., 2017). Lifestyle-related factors, for example physical activity, are associated with cognition in the elderly (Kimura et al., 2019). Evidence exists of many lifestyle factors that are potentially modifiable: cognitive activity, physical activity, social engagement, diet, smoking and alcohol consumption (Anstey et al., 2013) which may stabilize or improve declining cognitive function. These factors work via multiple mechanisms and are thought to either increase (smoking and alcoholism) or reduce (health diet and physical exercise) the risk of dementia. Another mechanism that scientists have proposed is that of cognitive reserve. It reflects the brain's capacity to provide a buffer against any brain pathology such that cognitive decline or dementia symptoms may manifest itself only when there is a greater threshold/burden of pathology (Clare et al., 2017).

1.2. NUTRITION AND BRAIN HEALTH: NEED FOR EVIDENCE BASED DATA

With the fast-evolving evidence on the various dimensions of nutrition and brain health covering the human lifespan, there is a need to document the available scientific evidence - based data. So far, the focus has been mainly on the role of nutrition on brain development in the early years. There is strong emerging need to identify the role of various lifestyle factors including diet and nutrition and physical activity on age related cognitive decline also. This will open up the use of new approaches for prevention, treatment or management of age-related disorders. Keeping this in mind, the findings are described in subsequent chapters.

1.3. METHODOLOGY

This review encompasses the role of dietary and nutritional factors as also lifestyle on brain development and brain health through the life course. Some of the areas covered include:

1. Importance of brain development and health.
2. Importance of first 1000 days in brain development.
3. Role of nutrients in brain development.
4. Importance of early life influences on cognitive development.
5. Factors affecting brain health through the life course. The areas to be discussed are: physical activity/ exercise, cognitively stimulating activities, sleep, nutrition, gut microbiome, and social connectedness
6. Risk factors for dementias.
7. Strategies to promote brain health.

1.3.1. Scope of the Study

The scope of this study is to encompass developments published at national and international level, particularly over the last 10 years. This status paper should provide a useful reference for defining future areas of research and planning in the area.

1.3.2. Search Strategy

This is a review regarding the association between nutrition and brain health. Studies were searched in PubMed and Google Scholar over the last 10 years, i.e., since 2011. Over 50 keywords were included in the search and have been described in ***Annexure I.***

The search was repeated until all search term combinations were performed. The results of the searches in Google Scholar were innumerable and it lacked the provision of filters (such as full-text articles, human studies, systematic reviews etc.) which made it difficult to review and hence, these results were excluded from the methodology.

1.3.3. Study Selection

The keywords were finalised after brainstorming and sharing with the stakeholders which were reviewed before finalising. It was decided that MeSH terms will be used for the keywords for conducting the search. Studies that were selected for the present review were

observational and intervention studies, review articles, systematic reviews and meta-analysis studies conducted on humans published in MEDLINE. These articles could be accessed with free full text in the English language. Articles that mentioned brain health or cognition and corresponding variable in either the title or abstract were initially included for full-text review. Based on this search, 612 articles were identified. In the second stage, the exclusion criteria as given below, was applied and 218 studies were selected. It was decided to examine a maximum of 75-100 full text articles for in depth analysis. Hence, finally 125 full text articles, after further filtering, were included for review (Figure 2).

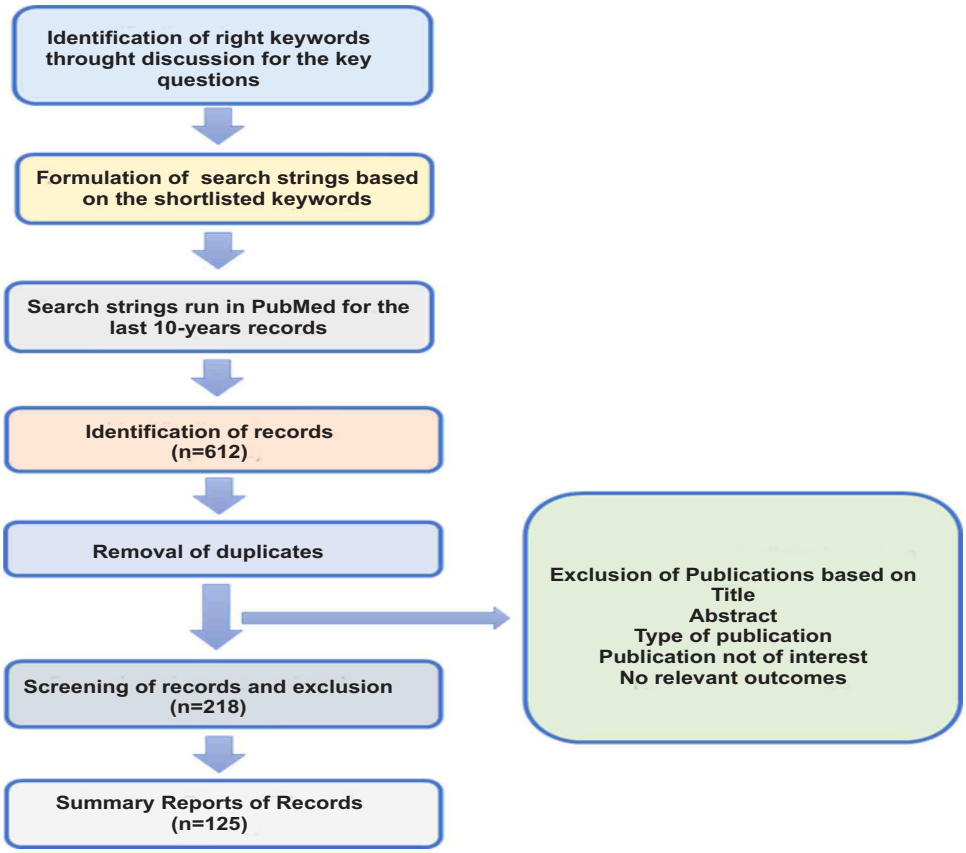

Figure 2: Flow Diagram of the Search Strategy and Study Selection Process

The articles were excluded after reading title, abstract, type of publication. Some other criteria included.

- Exclusion of data older than 2010.
- Exclusion of records with words like case reports, rats, animals, sheep, lamb etc in publication title.
- Exclusion of records based on animal studies.
- Exclusion of records with only basic research or conference proceedings etc.
- Exclusion of records of studies on psychological health like depression, anxiety, emotions, moods etc.

The findings are presented in the subsequent chapters.

2. PHYSIOLOGY OF BRAIN DEVELOPMENT

Brain development begins about 2 weeks after conception via processes of neurulation, proliferation, cell migration, differentiation, synaptogenesis, synapse pruning and myelination.

The first 1000 days, from pregnancy to first 2 years of life, harbours the greatest opportunity to provide optimal nutrition to ensure normal development of the infant. It is also the time of greatest brain vulnerability to any nutrient deficit.

Several nutrients play an important role in building the brain during pregnancy, infancy and early childhood. These include iron, protein, copper, folate, zinc, iodine and certain fats.

Undernutrition, overnutrition or obesity and unhealthy diets both in terms of unbalanced diets or diets contaminated with potential toxins are considered as "malnutrition" and have been shown to potentially reduce brain development.

Brain development is a protracted process that initiates at about 2 weeks after conception and continues into young adulthood, 20 years later. These processes interact with each other and have different dynamics and termination times: some are completed at birth, whereas others continue to develop throughout the lifespan (Figure 3). The neural tube is formed by 3–4 weeks of gestation, which then differentiates into the full nervous system between 4 to 12 weeks. Cells proliferate and give rise to neurons. From 12 to 20 weeks, these neurons migrate along the radial cells to their final destination and form the cortex. The first apoptosis occurs between 24 weeks into gestation and 4 weeks after birth, reducing the number of neurons by half. Concurrently, myelination begins at 29 weeks of gestation in the brain stem and develops primarily from inferior to superior and from posterior to anterior directions (Douet et al., 2014). Most of the axons are myelinated by early childhood, although myelination continues through adolescence and across the second and third decades of life (Blakemore 2012; Lebel et al. 2012). Synaptic proliferation and organization start at about 20 weeks of gestation, and synapses proliferate from birth to 2 years after birth. However, a regional reorganization occurs most predominantly during childhood and adolescence (Blakemore 2012).

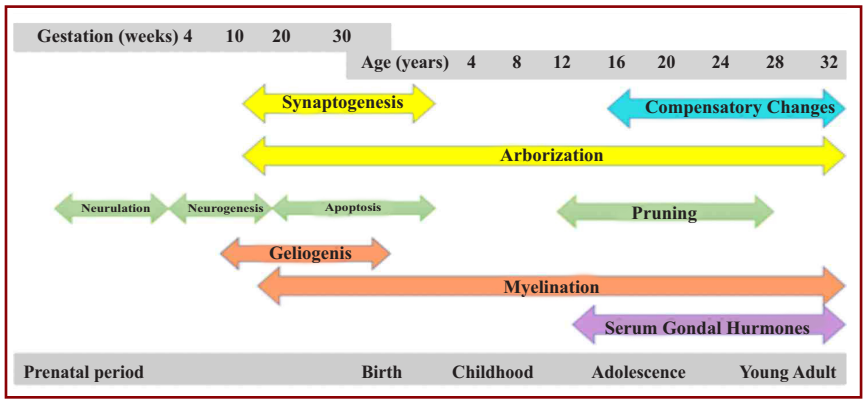

Figure 3: Key Events of the Human Brain Development

Source: Adapted from Douet et al., 2014

2.1. CRITICAL PERIODS OF BRAIN DEVELOPMENT

A longstanding controversy in psychology concerns the degree to which experiences in the early years are uniquely important in human development. Once the neuronal "foundation" is constructed in particular ways, subsequent revisions are more difficult to achieve. Irreversible changes in brain function occur during the critical periods. If a key experience does not occur during a critical period, behaviour is permanently affected (Nelson et al., 2019). In keeping with this assertion, a large section of literature has documented strong relationships between early adverse caregiving experiences and subsequent maladaptation. Timing of interventions designed to change young children's trajectories may reveal important differences in outcomes. Factors such as limited prenatal care, poor nutrition, exposure to nicotine, alcohol, or other substances are known to increase risk for adverse outcomes, and because they most often co-occur, the cumulative risk is even greater (Zeanah et al., 2011).

While the brain continues to develop and change throughout life, the last trimester of pregnancy and the first two years of life are rapid periods of brain growth and highest plasticity. The human brain at 5 months post conception is a smooth, bi-lobed structure resembling a coffee bean. By full term, it has gyri and sulci indicative of significant complexity, and looks more like the walnut-like adult brain. At birth, the rapidly developing brain areas include the hippocampus and the visual and auditory cortices. In the first year, there is rapid growth of the language processing areas as well as early development of the prefrontal cortex that controls higher functions such as attention, flexibility and inhibition.

The first 1,000 days are subjected to rapid rates of neuronal proliferation, growth and differentiation vis a vis complexity, myelination, and synaptogenesis for connectivity. Hence, during this period it is of utmost importance to provide optimal nutrition to ensure normal development. This period is also the time of greatest brain vulnerability to any nutrient deficit (Cusick and Georgieff, 2013).

All nutrients are important for brain development and function; optimal brain development depends upon providing adequate quantities of key nutrients during specific sensitive periods in these first 1,000 days. There is not a single common growth trajectory or single sensitive period - different regions (e.g., the hippocampus, cortex) and processes (e.g., myelination) of the brain exhibit different growth trajectories that peak at different times, each having specific nutrient requirements. A critical nutrient at one time may have little or no effect at another (Cusick and Georgieff, 2013).

Figure 4 illustrates the concept of critical periods. The X axis represents age and development, and the Y axis represents degree of neural plasticity. Multiple factors are presented in this figure. Firstly, there are the contributions early in life of genes that program brain development. Secondly, different domains (sensory, language, cognitive) have different trajectories of increasing and then diminishing plasticity suggesting different times when experience for these different domains will have their most profound impact. Finally, there are windows of plasticity or critical periods across these different domains of functioning.

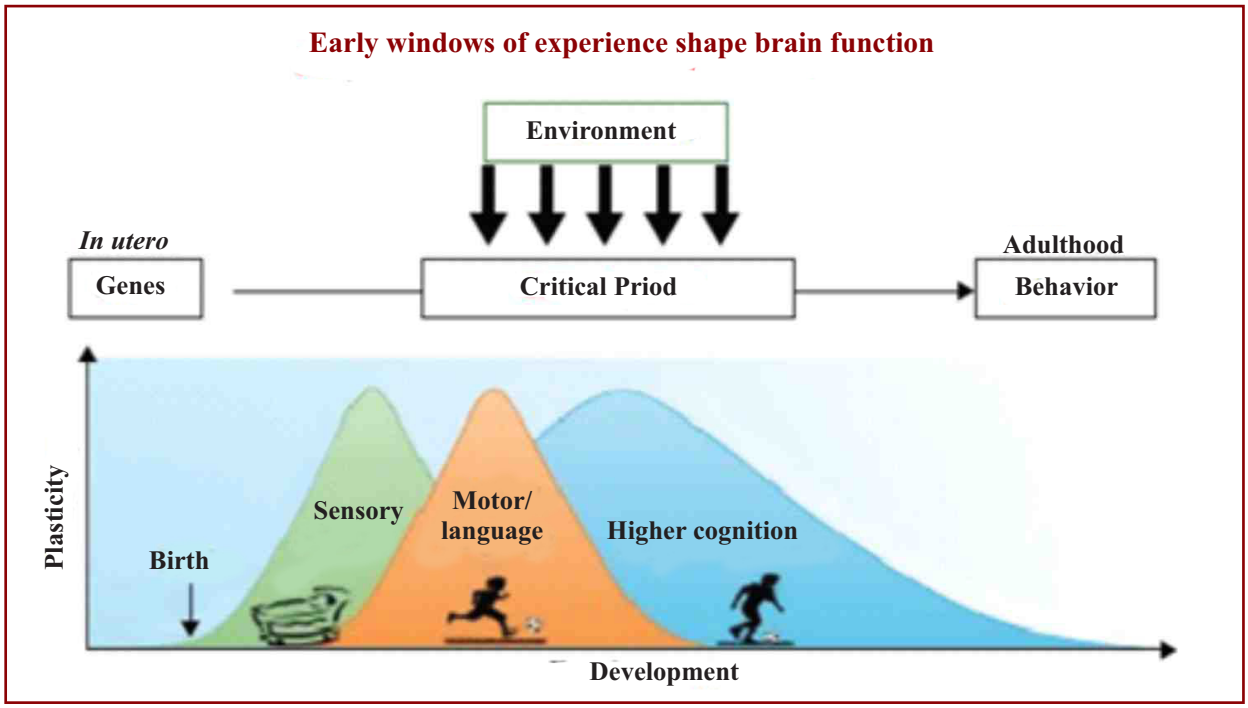

Figure 4: Interaction of Experience and Maturation during Critical Periods in Development.

Source: Figure is reproduced from Nelson et al., 2019 and Hensch and Bilimoria, 2012 (under the Creative Commons Attribution License/Public Domain).

The basic constituents for optimal child development are nutrition and health, hygiene, protection and responsive stimulation, together constituting 'nurturing care'. Healthy early child development is important for all children. The development of a child's brain depends on the environmental stimulation, particularly on the quality of care and interaction that the child receives. A baby who is hugged, comforted and visually stimulated has an advantage. Children who are nurtured and well cared for are more likely to fully develop cognitive, language, emotional and social skills; to grow up healthier, and to have higher self-esteem (UNICEF-India, 2020).

2.2. IMPORTANCE OF FIRST 1000 DAYS

The first 1,000 days of life, i.e. the time between conception and two years of age, is a unique period of opportunity when the foundations of optimum health, growth, and neurodevelopment are established. Yet in developing countries, poverty and malnutrition, weaken this foundation, leading to earlier mortality and significant morbidities such as poor health, and insidiously, substantial loss of neurodevelopmental potential. Presently, while undernutrition remains major challenge worldwide, certain populations are now being faced with the negative effects of overnutrition, obesity and risky nutrition in the form of unbalanced diets or diets contaminated with potential toxins. Each of these conditions has been shown to potentially reduce brain development (Cusick and Georgieff, 2013).

One of the most striking finding is that early life deviation from the expected trajectory due to a nutritional deficiency can affect brain function in adulthood, long after correction of the deficiency. While the young brain is plastic in its ability to recover from early insults, the window of opportunity narrows with advancing age. Evidence suggests that it is a far better policy to promote brain development through nutritional deficit prevention programs rather than to depend on replacement therapy once a deficit has occurred. Feeding the foetal, new-born, and young child brain is one of the best ways we can achieve this goal (Cusick and Georgieff, 2013). During the first 1,000 days, the brain grows more rapidly than at any other time in a person's life and hence needs the right nutrients at the right time to feed its rapid development.

There are *three crucial stages* during the first 1,000 days: pregnancy, infancy and young childhood. At each stage during the 1,000-day period, the developing brain is vulnerable to poor nutrition - either through the absence of key nutrients required for cognitive functioning and neural connections and/or through the "toxic stress" experienced in a situation of prolonged or acute adversity caused by food insecurity.

2.2.1. Pregnancy

During pregnancy, the human brain develops at a tremendous speed. At the 4th week of pregnancy, the infant's brain has an estimated 10,000 cells - by the 24th week, it has 10 billion. Nutrition drives this incredible transformation that a baby gets from his mother through her diet. Beginning in pregnancy, nutrients are needed for the creation of new neurons, responsible for transmitting and receiving nerve impulses, and for the covering of axons with myelin sheath, the fatty matter that accelerates the transmission of nerve impulses from one cell to another. Nutrients also fuel the formation of synapses which are the basis for learning ability. Several nutrients play an important role in brain development during pregnancy, including iron, protein, copper, folate, zinc, iodine and certain fats (NIH, 2011). Zinc, particularly, supports the development of the autonomic nervous system, the hippocampus and the cerebellum, while iron impacts the myelination of the nerve fibres which affects the brain's processing speed.

The mother's diet and her nutrient stores are the only source of nutrition for the foetus. When a pregnant woman is deprived of energy, essential nutrients or proteins that are needed for baby's development, the baby is placed at risk for developmental delays, birth defects and cognitive deficits. For example, when a woman lacks sufficient folic acid before becoming pregnant and in the early weeks of her pregnancy, the development of the neural tube can be affected, leading to congenital defects in the brain and spine (anencephaly and spina bifida) that can cause death or lifelong disability (Williams et al., 2015).

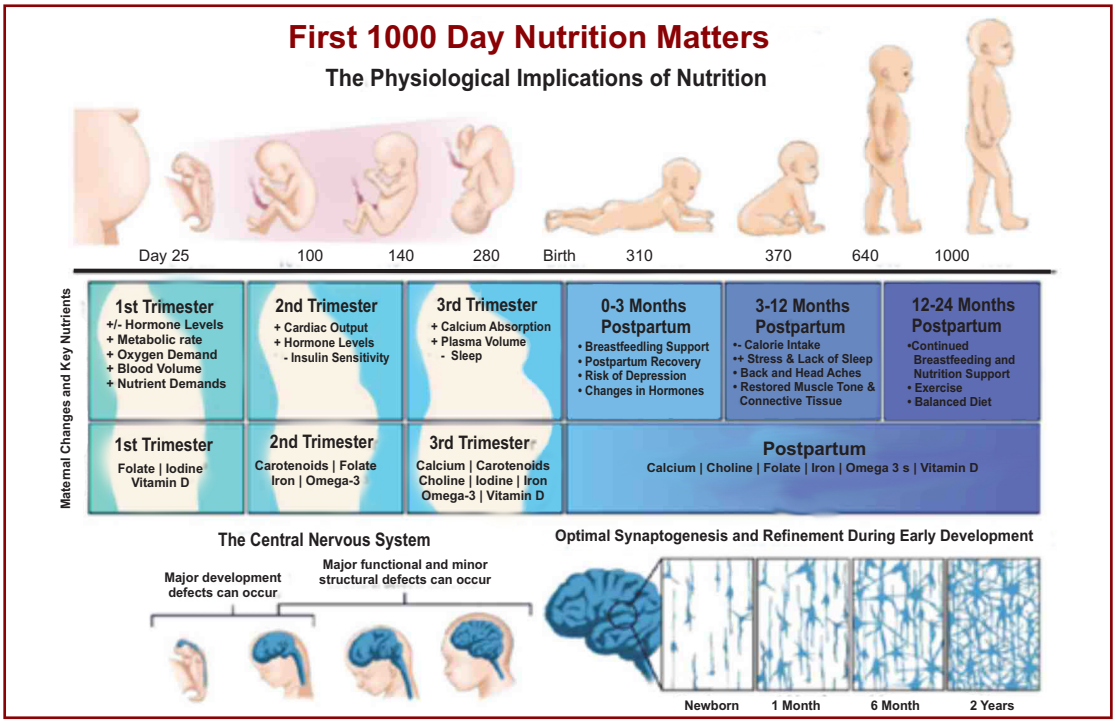

Figure 5: A Timeline of Critical Events during Pregnancy and Early Development, and the Role of Nutrition

Source: Beluska-Turkan et al., 2019

During gestation, non - nutritional factors, including maternal high blood pressure, diabetes mellitus and stress, can affect foetal brain nutritional status. In India, the incidence of low birth weight (LBW) and IUGR - LBW is over 20% leading to cognitive and neuro - developmental abnormalities. LBW babies are more likely to have lower scores on cognitive testing, school difficulties, gross motor dysfunction and behavioural problems (Murki and Sharma, 2014). Maternal stress directly affects the foetal brain and alters how certain nutrients are trafficked in the maternal-foetal dyad (Cusick and Georgieff, 2017; Monk et al., 2013). The body is susceptible to damage caused by internal and external harmful exposures (alcohol, medications, nicotine, environmental toxins), and these exposures can trigger major or minor functional and structural foetal defects (Figure 5).

2.2.2. Infancy

Infancy is also a time of rapid brain development and growth, mainly supported by the nourishment the baby receives. During this time, the brain is developing motor functions such as balance, coordination and posture. Breast milk is the ultimate superfood and its impact on brain development is unparalleled. Breast milk contains various nutrients, growth factors and hormones that are vital for a child's early brain development. Using neuroimaging technology, scientists have confirmed that children who were exclusively breastfed for at least 3 months (no food or liquids other than breast milk) developed increased white matter in several brain regions, which is associated with executive functioning, planning, social-emotional functioning and language (Deoni et al., 2013).

A study followed pre-term infants from birth until

later childhood and found that children who were fed more breast milk in the first 28 days had larger volumes of certain regions of the brain and by age 7, they had higher IQs and better scores in reading, mathematics, working memory and motor function tests (Belfort et al., 2016). Across all income levels, breastfeeding is associated with higher performance on intelligence tests among children and adolescents. Moreover, breastfeeding for more than 12 months is associated with a 3-point increase in IQ as well as higher educational attainment and income (Victora et al., 2015).

It appears that both breast milk and the quality of the breastfeeding experience contribute to the healthy development of a child's brain. Breastfeeding involves a great deal of mother-child interaction and nurturing and helps to strengthen a baby's sensory and emotional circuitry, which are critical for both cognitive and socio-emotional development. During foetal and early childhood development, the prefrontal cortex, hippocampus, and sensory systems undergo tremendous development that does not occur later in life (Schwarzenberg and Georgieff, 2018) (Figure 5).

As in pregnancy, reduction of non-nutritional factors that affect nutrient absorption and distribution to the brain is crucial in the postnatal period. These include maternal high blood pressure, diabetes mellitus, stress, infection and inflammation, which significantly affect how protein, zinc and iron are processed (Cusick and Georgieff, 2017). Ten percent of pregnancies are complicated by pre-gestational or gestational diabetes mellitus; up to 65 % of infants of diabetic mothers are born with iron stores below the 5th percentile. Maternal stress not only has a direct effect on the foetal brain, but also alters how certain nutrients are trafficked in the maternal-foetal dyad. In the case of iron, infection increases levels of hepcidin, which reduces iron absorption, sequesters iron in the reticulo-endothelial system, and results in functional iron deficiency (Cusick and Georgieff, 2017).

2.2.3. Early Childhood

In the toddler stage, the child's brain continues to grow and develop at a rapid pace. The speed of a child's neural processing -i.e., how quickly the brain can interpret and relay information - also increases dramatically during early childhood, facilitating the brain to perform more complex tasks. During this period, a young child's brain is busy forming synapses - connections that allow neurons to communicate with one another. Throughout early childhood, synapses are created at a rate faster than at any other time in life and a toddler's brain has twice as many synapses as he/she will have in adulthood (Figure 5). The excessive synapses produced by a child's brain during this period make the brain neuroplastic i.e. very responsive to external input and enables human beings to adapt to changing environments and circumstances. In the second year, synapses in the brain's language areas are developing and becoming more interconnected, leading to a tremendous surge in a child's language abilities.

Nutrition during this period remains critically important. Protein, iron, zinc and iodine are essential for the toddler's rapidly developing brain. Other factors in the children's environment can also negatively effect brain development. The plasticity of the young child's brain makes it particularly sensitive to elevated levels of stress hormones that can harm its developing architecture (Shonkoff and Garner, 2012).

Continued exposure to high levels of stress, like that experienced by food insecure families, can alter a young child's stress response system, leading to heightened arousal, which increases the risk of stress-related disorders later in life (CDCHU, 2014).

Children, 1 to 3 years old, are particularly vulnerable because they typically ingest a diet similar to that of their adult parents. Thus, they are susceptible to poor parental food habits and can have food insecurity that causes a sacrifice of quality food for food quantity (CCPCN, 2015). In low- and middle-income countries children between 1 and 3 years of age are at high risk of nutritional deficiency because the local cereal-grain-based-diet is insufficient to meet the substantial nutrient requirements needed to sustain their rapid growth. Food insecurity, or inadequate food due to lack of money or other resources, needs to be addressed, thus helping to ensure optimal nutrition and brain development from pregnancy though early childhood (Cusick and Georgieff, 2017).

The prevalence of stunting reaches a peak around 18-24 months, after which age corrective interventions do not have an effect. The causes are multiple and include poor adolescent and maternal nutrition, inadequate and inefficient infant and young child feeding (IYCF), limited or inappropriate knowledge about mother and child caring practices, limited access to available services as reported by Akshay and Anand (2019). Their study on mother and child healthcare practices in a rural district in Haryana reported that early age of marriage and child bearing, illiteracy and unawareness, preference for a male child, traditional and religious norms, patriarchal family structure and resultant gender dynamics have led to poor maternal and child care especially in the first 1000 days. Infants and young children are more likely to get diarrhoea and other infections with poor hygienic practices in food handling and feeding, further leading to growth failure and poor development. Deworming and iron supplementation protect against iron loss, which is essential for optimal growth and development as anaemia poses devastating consequences for children's brain development (UNICEF - India, 2012).

2.3. BEYOND 1000 DAYS

Recent studies using brain imaging techniques confirmed that the brain develops throughout childhood and young adulthood, and that the various brain structures follow different trajectories of development and maturation (Lebel et al. 2012). Nutrients affect neuroanatomy, neurochemistry, and neurophysiology, cumulatively influencing neuronal performance through all life-cycle phases. As discussed, there is established evidence for the importance of nutrition early in life. Beyond 1000 days, during early and middle childhood, synapses are rapidly created and later during adolescence are removed selectively, necessitating a steady supply of nutrient intakes (Prado and Dewey, 2014). Waves of brain development continue through adolescence, in particular those related to higher cognitive functioning (Black et al., 2017). During adulthood, evidence points to the need for several nutrients to support neuroplasticity and behaviour and to diminish the negative effects of aging in the brain (Goyal et al., 2018).

3. ROLE OF HEREDITY AND ENVIRONMENT IN COGNITIVE DEVELOPMENT

Studies have attempted to examine the complex interactions between genes, environment and the developing brain. Data clearly indicates that brain development is under tight genetic control across the lifespan.

Of the whole human genome, 10,000 genes (approximately one-third) are only expressed during brain development. All cognitive domains show some degree of heritability, which supports genetic influences leading to individual differences in human cognitive abilities.

Genetic variations interact with exposure to early life adversities and affects child's brain development mainly through epigenetic mechanisms.

Experiences during early development have powerful effects on brain function, leading to individual differences that could contribute to poor brain development, behavioural dysfunction and risk for chronic diseases over the lifetime.

Brain development occurring during the prenatal months is majorly under genetic control. According to Bueno (2019), cognitive functions, such as working memory, cognitive control, attention, intelligence, other executive functions, and other related functions such as motivation and resilience, develop through the brain's activity, which depends on neural connectivity and function. The construction of the brain and the functioning of neurons rely on genetic programs, so genes influence the cognitive functions involved in learning processes.

3.1. ROLE OF GENES

The human genome comprises around 20,300 genes (Salzberg, 2018), all of which present genetic variants or alleles. However, 10,000 genes are only expressed during brain development (Zhang et al., 2011). The alleles contain different nucleotide sequences implying differences in the message they encode, and by synthesizing the corresponding proteins, they influence the biological functions or characteristics. Individual variations due to genetic influences are found in physical and psychological traits, including those related to cognitive functions. Davies et al (2018) identified 148 novel independent genes, besides the 709 previously identified, associated with general cognitive functions; meanwhile, Zwir et al (2018) identified 736 genes that are significantly associated with temperament (Bueno, 2019).

Heritability is expressed on a scale from 0 to 1 or as a percentage from 0 to 100%. A value of 0.0 (0%) is interpreted as a trait where the observed differences are not associated with the genetic variation but only with environmental differences. Conversely, a value of 1.0 (100%) is interpreted as a trait in which the observed differences are solely due to genetic variation and not environmental differences. An attribute

may have complete heritability (1.0) under specific environments yet be altered drastically by environmental changes. For example, with normal food intake, PKU has a heritability of 1.0, but dietary interventions from birth that reduce phenylalanine intake make phenotypical consequences negligible. Hence, if conditions change, the heritability also changes. Increasing environmental variation may reduce the proportion of the phenotypic variance due to genetic diversity (Bueno, 2019).

In a review by Hermo et al (2014), all the cognitive domains (intellectual ability, performance ability, verbal abilities, memory, processing speed) showed some degree of heritability, which supports that genetic influences lead to individual differences in human cognitive abilities. The range of heritability for measures of *general intelligence* varied from 66% to 87%; for *performance intelligence*, from 43% to 83%; for *verbal ability*, from 26% to 85%; for *memory*, from 40% to 54%; for *speed of information processing*, from 24 to 70 %, *visuospatial memory*, from 19 to 46%; for *executive control*, from 36 to 75%. Attention control and interference resistance tasks have moderate values of heritability, varying from 38% to 53%. The highest estimates for the executive control component of working memory corresponded to 66%.

Change in gene expression is fastest in the human brain during foetal development, slows through childhood and adolescence, and stabilizes through adulthood, and then speeds up again after age 50. Genes with high expression during foetal development have the most significant decreased expression in the ageing cortex. In contrast, genes with low expression during foetal development show increased expression in ageing and neurodegeneration (Colantuoni et al., 2011).

3.2. ROLE OF ENVIRONMENT

Gene-environment interactions account for a large portion of the individual differences contributing to behavioural dysfunction and risk for chronic diseases over the lifetime. Individual differences, mainly through alterations of the DNA structure and chromatin function can affect gene expression. These epigenetic changes regulate the operation of the genome and can have an impact on the development of brain structure and function, especially during early life (Miguel et al., 2019). They act as markers for lasting effects of the early environment and contain a 'molecular memory' of the early exposure in children. In neonates, the genotype alone, in 25% of cases, accounts for variably methylated regions. The best explanation for 75% of the variation in methylated areas is the interaction of genotype with different in utero exposures, including maternal smoking, maternal depression, maternal BMI, infant birth weight, gestational age and birth order (Teh et al., 2014).

3.3. EARLY LIFE INFLUENCES ON BRAIN DEVELOPMENT AND FUNCTION

Environmental exposures during the first years of life permanently modify brain structure and function through epigenetic pathways and consequently affect the susceptibility to mental disorders. These brain changes could affect socio-emotional outcomes, behavioural dysfunctions, and the risk for mental health problems (Miguel et al., 2019).

Prenatal Factors: An adverse intra-uterine environment is reflected in poor foetal growth and prenatal influences on brain development and behaviour have been extensively studied. Foetal growth is influenced by maternal, placental, and genetic factors. Maternal influences include maternal age, socio-economic status, maternal health, substance use and nutrition (Miguel et al., 2019). Placental dysfunction leads to a poor supply of nutrients and oxygen to the foetus and foetal malformations are also important factors that affect foetal growth. Poor intrauterine growth is associated with delays in development and an increased risk for several mental health problems (Miguel et al., 2019; Mathewson et al., 2017).

It is well-known that substance abuse impacts neurodevelopment (Ross et al., 2015).Intrauterine exposure to tobacco lowers the relative gene expression of selected foetal brain regulatory genes responsible for brain growth, myelination, and neuronal migration altering brain structure and function (Salihu et al., 2017). The long-lasting behavioural impairments associated with prenatal smoking include reduction in cognitive and motor functioning, impaired mental development and enhanced risk for bipolar disorder, depression, and addiction (Webby et al., 2011) and attention-deficit/ hyperactivity disorder in the offspring (Dong et al., 2018).

The literature extensively documented the effect of psychological stress and altered maternal mental health on the offspring. A systematic review of observational studies in South East Asia reported that exposure to mental stress in early pregnancy and antenatal stress affect both cognitive and motor development in infants (Venkatesh et al., 2019). However, another systematic review and meta-analysis of maternal mental health interventions in low- and middle-income countries did not report an impact of these interventions on either cognitive or psychomotor development (Tol et al., 2020). Traumas such as the death of a family member, disasters such as earthquakes and chronic stressors like homelessness, poverty/crime, unemployment or discrimination, during gestation affect pregnancy duration, birth weight (Dunkel Schetter and Tanner, 2012) and affects offspring neurodevelopment, neurocognitive function, cerebral processing and functional and structural brain connectivity. These changes increase the risk for behavioural and mental health problems later in life(Miguel et al., 2019; Adamson et al., 2018; Qiu et al., 2015).

Perinatal Factors: Perinatal hypoxia-ischemia/hypoxic-ischemic encephalopathy is the most common cause of morbidity and mortality in human neonates; around 5-10% of the surviving infants demonstrate persistent motor deficits, and 20-50% exhibit sensory or cognitive abnormalities that persist to adolescence (Millar et al., 2017). However, subtle cognitive impairments, including hyperactivity, inattention, and poorer cognitive ability, can be found in the absence of significant neuromotor impairment (Miguel et al., 2019). A meta-analysis on 45,821 individuals with attention-deficit/hyperactivity disorder and 9,207,363 controls suggests that conditions such as preeclampsia, breech/transverse presentations– all of which involve poor oxygenation during delivery – are significantly associated with attention-deficit/hyperactivity disorder (Zhu et al., 2016).

Postnatal Factors: The quality of the postnatal period has a profound effect on a wide range of neurodevelopmental outcomes. Experiences in terms of nature and timing drive much of postnatal brain development. The absence of key experiences during the critical periods can exert severe and, in some cases, lasting effects on multiple domains of development including behaviour. Psychological neglect early in life has a profound effect on cognitive development (Nelson et al., 2019).

High rates of post - traumatic stress symptoms, depression, anxiety, and substance use disorders are associated with exposure to traumatic occurrences such as child abuse, bullying, terrorism, war and violence (Miguel et al., 2019). Exposure to trauma in childhood activates the stress response systems and dysregulates serotonin (5-hydroxytryptamine) transmission that adversely impacts brain development. Smaller cerebral, cerebellar, prefrontal cortex, and corpus callosum volumes, as well as reduced hippocampal activity, were reported in maltreated young people (De Bellis and Zisk, 2014). Orphanage rearing is associated with decreased autonomic and hypothalamic-pituitary-adrenal axis responses to psychosocial stress, enlarged amygdala volumes, and accelerated amygdala-medial prefrontal cortex connectivity mediated by cortisol (Miguel et al., 2019; Gee et al., 2013). Recent evidence also reveals a significant, negative association between nutrition intake and learning - surprising among children from low - income group families or low resource settings (UNICEF, 2019). Evidence suggests associations between low SES in early childhood and smaller grey matter volume in the hippocampus (Hanson et al., 2015; 2013; Noble et al., 2015). Combined with low frontal and temporal lobe volume, this might mediate associations between poverty and low cognitive, academic, and behavioural performance (Hair et al., 2015).

Other environmental influences which could adversely affect brain development in young children are disturbances of maternal mental health which reduce maternal sensitivity and engagement (Rifkin-Graboi et al., 2015). Nguyen et al.(2018) reported that physical or cognitive-developmental deficits in the offspring were associated with different threshold levels of depressive symptoms in mothers . Several studies have highlighted that maternal deprivation led to developmental delay in children (Curly and Champagne, 2016; Routray et al., 2015) and maternal caregiving is positively associated with multiple domains of early child development (Black et al., 2019). Studies also suggest that the basic brain structure and function are affected by early institutionalization experiences (Nelson et al., 2019; Vanderwert et al., 2016; Hodel et al., 2015; Sheridan et al., 2012), which improve when the children are shifted to foster care (Bick et al., 2015; McLaughlin et al., 2015; Fox et al., 2011; Windsor et al., 2011; Zeanah et al., 2011).

Parental behaviour, parent-child and sibling relationships play an essential role in children's physical, cognitive, and mental development, as well as future patterns of brain development during adolescence. Research has also documented the link between parental behaviours and brain structure and function in children (Richmond et al., 2019; Whittle et al., 2017; 2014; (McHale et al., 2012). Black et al (2021) reported that early nurturing home environments protect young children against the effects of early adversities on their IQ during adolescence. The low-cost home-based activities that promote early development are storytelling, singing, and playing with household objects by exposing young children to experiences (Black et al., 2017).

Cognitive enrichment early in life provides the foundation for continued intellectual stimulation across the life course, resulting in improved cognitive functioning in late adulthood. School closures resulting from the pandemic could have a lasting impact on children's development, and it has been suggested that parents provide their children with a holistic learning environment.

Breastfeeding may improve cognitive development through several mechanisms related to the composition of breast milk and the experience of breastfeeding (Prado and Dewey, 2014). A meta-analysis of 17 studies on the relationship between breastfeeding and

intelligence reported that breastfed subjects had a higher IQ by 3.44 points or 2.62 points when controlled for maternal IQ (Horta et al., 2015). The cognitive benefits of breastfeeding reportedly continue into adulthood.

There is also emerging evidence to support a positive relationship between physical activity and fitness, cognitive function and academic achievement (Drollette et al., 2019; Egger et al., 2019; Chaddock-Heyman et al., 2019; Martin et al., 2018; Marques et al., 2018; Desai et al., 2015; Jacob et al., 2011). Moreover, a few studies have reported improvements in cognitive performance on performing yoga (Telles et al., 2013; Chaya et al., 2012). Sleep health - as indicated by the duration, timing, and quality of sleep and the presence of sleep disorders - is an additional modifiable aspect of children's functioning, with critical connections to children's learning and development. Research has revealed that sleep has a vital role in physical and mental health and wellbeing, including cognitive function (Bernier et al., 2017), expressive and receptive language (Botting et al., 2017), and social and emotional function (Cremone et al., 2018).

Play is an integral part of a child's lifestyle. Play-based learning stimulates the development of the brain via multiple hands-on activities (digital/non-digital), allowing a child to explore, imagine, create, experience and make errors. Play-based learning not only helps pre-schoolers attain pre-language, pre-math, and cognitive skills but also helps develop fine motor, gross motor, social and emotional skills (Kalra, 2021). In fact, playing video games affects those regions of the brain responsible for reward, impulse control and sensorimotor coordination (Weinstein and Lejoyeux, 2015) and is also associated with better working memory and spatial skills related to science, technology, engineering and mathematics performance (Uttal et al., 2013). Also, parent-child co-play intersects with larger patterns of parent-child closeness, communication, and parental involvement in child learning (Blumberg et al., 2019; Wang et al., 2018).

Children who undergo musical training have better reading ability, verbal memory, accuracy in second language pronunciation, and executive functions. Learning to play an instrument in childhood may predict academic performance and IQ in early adulthood. The effect on cognitive development depends on the timing of musical initiation (sensitive period) and several other modulating variables (Miendlarzewska and Trost, 2014).

Decades of research outline two significant points regarding the influence of media. Firstly, the effects depend on the content of the programmes. For example, while preschool educational television viewing has long-term positive associations with academic achievement in English, Maths, and Science (Fisch et al., 2014), exposure to violent or even solely entertaining television is negatively associated with cognitive development (Blumberg et al., 2019). Evidence links longer duration of television viewing during childhood to poorer language, literacy and cognitive skills (Hutton et al, 2020; Takeuchi et al., 2015). Regions of the brain that are associated with social memories and cognition and imitation showed higher levels of activation on exposure to social media (Sherman et al, 2016).

Hence, while genetic predisposition is crucial for brain development, experiences during early development in the child will have powerful effects on brain function, leading to individual differences that could contribute to behavioural dysfunction and increased risk for chronic diseases over the lifetime. Nutrition is an important modulator for early brain development often over and above the environment the child is exposed to.

4. ROLE OF NUTRITION IN BRAIN DEVELOPMENT AND FUNCTION

The modifiable lifestyle factor that is intensively researched in relation to aging brain and neurodegenerative diseases is diet; specifically

- Various macro- and micro-nutrients
- Dietary patterns and related food groups
- Other dietary components

Implications of nutritional deficiencies on brain development and function in mother and child are severe.

Increasing evidence is showing a significant influence of the gut microbiome on brain development and function

Improving nutrition during the first 1000 days of life has been given considerable attention in recent years. Brain growth rate is very high during this period, falling rapidly as childhood begins. Aerobic glycolysis accounts for approximately 30% of the human brain's glucose consumption rate in the early years compared with about 10% at age 30, pointing to the critical metabolic requirements of the brain that continue well beyond the first 1,000 days, arguing for an expanded view on the nutritional requirements of the developing human brain. Synapses are created during childhood and selectively removed during adolescence, requiring appropriate nutrition. In addition, brain development occurs in phases in adolescents, especially those related to higher cognitive functioning. Furthermore, nutrients are needed to maintain neuroplasticity and reduce brain ageing during adulthood and old age (Goyal et al., 2018).

4.1. ROLE OF NUTRIENTS ON BRAIN DEVELOPMENT AND FUNCTION

Nutrients are bioactive molecules that are crucial for good health and functioning in humans. Most nutrients need to be obtained through the diet as the body cannot synthesize them. The brain is a high-maintenance complex organ as it requires a high turnover of nutrients to function optimally. Various nutrient-specific transport systems and physiological mechanisms continuously work to replenish the nutrients that the brain utilizes (Morris, 2012).

All nutrients are essential for the growth of the brain; however, certain nutrients have a profound effect during early brain development. Table 1 summarizes the critical processes during neural development and the nutrients which contribute to these developmental processes. The impact of their deficiency on the developing brain will depend upon what process the nutrient is essential for and whether its deficit coincides with a critical/sensitive period of that process of brain development (Cusick and Georgieff, 2017). Several studies have reported on the impact of early nutrition on postnatal head growth and later neurodevelopment in preterm infants (Morgan et al., 2014; Cormack and Bloomfield, 2013; Ehrenkranz et al., 2011).

Table 1: Critical Processes during Neurodevelopment Affected by Specific Nutrients

Cell Type	Function	Nutrient Example
Anatomy		
Neuron	Division (Neurogenesis) Migration Differentiation (Neurite Outgrowth; Synaptogenesis)	Protein, Carbohydrates, Iron, Copper, Zinc, LC - PUFA, Iodine, Vitamin A, Vitamin B_6, Vitamin D, Vitamin C
Oligodendrocyte	Myelination	Protein, Carbohydrates, Iron, Iodine, Selenium, Zinc, Vitamin B_6 , Vitamin B_{12}
Chemistry		
Neuron Astrocyte	Neurotransmitter Concentration, Receptor, Reuptake	Protein, Iron, Iodine, Copper, Zinc, Selenium, Choline, Vitamin B_6, Vitamin D
Physiology and Metabolism		
Neuron Oligodendrocyte	Electrical Efficiency	Glucose, Protein, Iron, Iodine, Zinc, Choline, Copper

Source: Cusick and Georgieff, 2017

4.1.1. Macronutrients that Affect Brain Development, Function and Decline

Dietary intake affects brain development and function in two ways - the use of metabolic energy from macronutrients such as carbohydrates, proteins, and fats and the availability of individual micronutrients from foods (i.e., folate, iron, and iodine) (Derbyshire, 2018). The brain has high metabolic activity due to its complex structure and processing demands throughout life. ***Annexure 2*** gives a compilation of studies related to macronutrients and brain development and function.

The relationship of undernutrition and congnitive development in early life has been well documented. General malnutrition during foetal development and the initial months of life show life-long deleterious impacts on brain development that later manifest in learning difficulties (e.g., self-regulation difficulties and lower academic achievement) (Jirout et al., 2019). In a study by Sokolovic et al. (2014), continued stunting status between 6 and 12 years was associated with lower scores on multiple cognitive tests such as memory, mental speed, retrieval ability and visuospatial ability in Indian children. Stunting and underweight were associated with low reading and math scores and lower grade level in a study in South Indian children (n=1194, age=8-11 years), as Acharya and colleagues (2019) also reported.

One of the most common indicators of malnutrition worldwide is growth failure in the foetus, referred to as Intrauterine Growth Restriction (IUGR), compromising multiple

nutrients (both macro-and micro). This leads to poor developmental outcomes due to protein or energy undernutrition, micronutrient deficiencies or both. Scientists agree that IUGR and growth failure in the first 3 years have a profound effect on neurodevelopment; specifically, in the achievement of full developmental trajectory, brain size, reduced RNA and DNA contents, fewer neurons, fewer neurotransmitters and growth factors and simpler dendritic and synaptic head architecture (Cusick and Georgieff, 2017). At the brain level, lack of protein results in a series of negative effects including changes in protein phosphorylation, impaired neurotransmitter systems, decreased overall brain volume, and altered hippocampal formation (Jirout et al., 2019).

However, a Swedish prospective cohort study did not find any correlation between protein and energy intake and brain volumes at term equivalent age or neurodevelopmental outcome at 2 years corrected age. A positive correlation was seen between insulin-like growth factor-1 (IGF-1) and cerebellar, grey matter, unmyelinated white matter volume, total brain volume and mental development, concluding that nutritional intake alone might be insufficient to alter postnatal growth restriction associated with impaired brain growth (Hansen-Pupp et al., 2013; 2011).

Jirout et al (2019) reported that long-chain polyunsaturated fatty acids (LCPUFAs) supplementation during gestation might improve crystallized intelligence in children while saturated fatty acids intake is negatively related to memory. LCPUFA supplementation presented inconclusive results in pregnant mothers; however, clinical trials in children and older adults showed improvement in specific domains of cognition, better IQ, visuo-perceptive capacity and executive functioning (Portillo-Reyes et al., 2014). Interestingly, two large systematic analyses by Delgado-Noguera et al (2015) and Gould et al (2013) concluded that data on Omega-3 LCPUFA supplementation to pregnant and breastfeeding mothers to improve neurodevelopment or visual acuity in the offspring is inconclusive.

In the meta-analysis by Coelho-Junior and colleagues (2021), no significant associations were observed between protein intake and global cognition in old age. However, memory and protein intake were positively correlated in 3 studies. Visuospatial, verbal fluency, processing speed, and sustained attention were each positively associated with protein consumption in only one study. A cross-sectional study by Li et al. (2020) found a positive association between dietary protein and cognition. They reported that protein intake from total animal foods, total meat, eggs and legumes were associated with better performance on specific cognitive tests.

Various studies on adults and elderly have suggested that a high-fat diet has adverse effects on cognition. Okereke et al (2012), based on a longitudinal study on 6183 elderly females in the US, reported that high amounts of saturated fatty acids were associated with worse cognitive and verbal memory trajectories, whereas higher MUFA intake was related to better trajectories. A review by Francis and Stevenson (2013) reported an association between HFS diet (high in saturated fat and refined carbohydrates) and impaired cognitive function. Acute consumption of high-fat diet primes the hippocampus to produce a neuroinflammatory response to a mild immune challenge, causing memory deficits (Spencer et al., 2017). A high-fat diet increases the risk of obesity, increased chances to develop diabetes and the development of cognitive deficits and perhaps Alzheimer's disease (AD). Insulin resistance, impaired glucose metabolism, and type 2 diabetes mellitus are well-known risk factors for AD.

Polyunsaturated fatty acids (PUFAs) regulate the function and structure of neurons, endothelial cells and glial cells in the brain. The omega-3 fatty acids - eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), also modify neurotransmission, reduce neuroinflammation and promote neuronal survival and neurogenesis (Bazinet and Layé, 2014). DHA is critical for neurogenesis and neuronal migration, synaptogenesis and membrane fatty acid composition and fluidity, affecting the neurotransmitter systems, particularly the visual system, areas of the brain that mediate attention, inhibition and impulsivity (Cusick and Georgieff, 2017). PUFAs have a role in maintaining cognitive function and preventing dementia due to their anti - thrombotic and anti-inflammatory properties and also affect neural processes (Gillette - Guyonnet et al., 2013). Further, cognitive decline in later years, is associated with a high energy intake from fat and protein and low energy intake from carbohydrates as reported in a retrospective study in China (Ding et al., 2018) . Low dietary intake of omega - 3 PUFAs can also contribute to memory loss (Spencer et al., 2017).

4.1.2. Micronutrients that Affect Brain Development, Function and Decline

Micronutrients facilitate the body to produce enzymes, hormones, and other essential substances for proper growth and development (WHO, 2021). Iodine, vitamin A, and iron are most crucial in terms of global public health as their deficiency represents a major threat to the health of populations worldwide, particularly children and pregnant women in low-income countries (WHO, 2021). While the role of B group vitamins in brain development has been explored in recent years, not much evidence has emerged in the last decade on the association of fat soluble vitamins and cognitive development in early life. Most studies have focussed on the role of the latter in cognitive decline.

B-vitamins are essential for brain development and function through many mechanisms. A review by Venkatramanan et al (2016) reported that the importance of adequate **vitamin B_{12}** status, particularly during pregnancy and early childhood, cannot be overemphasized in light of the role of vitamin B-12 in the neural myelination, brain development and foetal and child growth. Ars and colleagues (2019) studied prenatal **folate, homocysteine** and vitamin B_{12} levels and child brain volumes, cognitive development, and psychological functioning in 256 Dutch children aged between 6 and 8 years. They reported that low prenatal folate levels were associated with a smaller total brain volume and predicted poorer performance on the language and visuospatial domains. They also suggested that folate insufficiency in early pregnancy has a long-lasting effect on brain development and with homocysteine levels is associated with poorer cognitive performance.

According to a review by Naninck et al (2019), the findings were mixed among the included human observational studies. About half of the studies showed beneficial associations between adequate maternal folate status and offspring cognitive performance, and half of the studies showed no significant associations. The majority of the observational studies on maternal folate intake suggest a positive association with child cognitive function. Only one RCT on maternal folic acid supplementation during late pregnancy and offspring cognitive performance was identified, providing insufficient evidence for a causal relation between maternal folate and childhood cognitive performance. In contrast to the animal studies, no effect of maternal folate status or intake on new born DNA methylation level of foetal growth and neurodevelopmental genes was observed in the only human study on this subject matter.

A study in Israel demonstrated language deficits in 5–7-year-olds fed **a thiamine** deficient formula during infancy. These children showed impaired language ability compared to the controls at 5 years of age, even though they had no neurological symptoms during infancy (Fattal et al., 2011).

Studies assessing the association of B vitamins and cognition in the elderly were inconclusive (Agnew-Blais et al., 2015; Dangour et al., 2015; Doets et al., 2013). Only one study on US adults showed an association of vitamins (**niacin, folate, B_6 and B_{12}**) with better cognitive function in midlife. In postmenopausal women free of MCI, low folate intake may increase the risk of MCI/dementia in later life.

A role for **vitamin D** in the maintenance of brain health and cognition is emerging with reports that serum 25 - hydroxyvitamin D [25(OH) D] levels are lower in those with impaired cognitive function and AD than healthy controls (Goodwill and Szoeke, 2017; Afzal et al., 2014) and low vitamin D levels increase AD risk 7 years later (Annweiler et al., 2011). In an 18-week study comparing high-dose vitamin D3 (4000 IU/day) to a low dose (400 IU/day) in 82 healthy adults, the high-dose supplementation improved visuospatial memory but no other cognitive domains (Pettersen, 2017). Few studies on the effect of Vitamin D and cognition are elaborated in ***Annexure 3***. In a review by Annweiler et al (2013), executive dysfunction was predicted by lower serum 25(OH)D concentrations while its association with episodic memory was inconclusive. In a meta-analysis, cognitive impairment was observed in patients deficient in vitamin D (Etgen et al., 2012). A systematic review by van der Schaft et al (2013) reported that poor outcome in various cognitive tests was linked to a higher dementia incidence risk in patients with low 25 (OH)D. Hypovitaminosis D was also associated with a subjective cognitive complaint that predicts cognitive decline and dementia (Landel et al., 2016).

While many studies show a reduced risk of cognitive decline, with intake of **antioxidant vitamins (E & C),** mixed results have been reported, as evident in ***Annexure 3***. The use of vitamin E and C supplements showed a reduced risk of cognitive decline in a prospective cohort in Canada (Basambombo et al., 2016). Studies also reported no association (Nooyens et al., 2015) or inverse association (Galasko et al., 2012) with antioxidants and cognition. A cross-sectional US-based study associated a high intake of vitamin E with a higher score on verbal memory, immediate recall, and better language/verbal fluency performance (Beydoun et al., 2016).

A cross - sectional study (Chouet et al., 2015) in 192 French elderly reported that higher dietary **phylloquinone** (vitamin K) was associated with better cognition and behaviour among older adults aged $\geqslant$65 years.

4.1.3. Minerals and Trace Elements that Affect Brain Development and Function

Iron is an essential component of the haemoglobin molecule, which transports oxygen to all the body's organs, including the brain. Iron deficiency anaemia (IDA) is a well-known risk factor for short-term and long-term cognitive impairment. IDA during infancy is associated with poor mental and motor development and, during later childhood, with poor cognition and school achievement (Prado and Dewey, 2014). More than 50 studies in humans, including observational studies, supplementation trials, and iron therapy studies, demonstrate a crucial role of iron in brain development (Cusick and Georgieff, 2016). Collectively, there is a consensus that supports the principle that prevention is preferable to treating iron deficiency and that the earlier the brain is protected from suboptimal iron status, e.g., the prenatal period and early infancy, the better it is (Cusick and Georgieff, 2012). Brain iron deficiency is associated with disruption of neurophysiological mechanisms that do not provide regular stimuli and compromise motor

and cognitive development (e.g., impaired motor sequencing and bi-manual coordination, poor executive function, attention, and memory).

On the other hand, brain iron overload also impairs neurophysiological mechanisms (e.g., exacerbated brain oxidative stress, neuronal cell death), and is associated with motor and cognitive declines (e.g., motor slowing, insufficient adjustment and altered feedback processing and sensitivity, memory loss, and impaired decision-making) (Ferreira et al., 2019). ***Annexures 4 and 5*** outline the characteristics of human studies elucidating the role of micronutrients (minerals) in cognition. The table gives mixed results for all the micronutrients, including iron. Moreover, mis-timed or excessive iron intake may lead to worse neurodevelopmental outcomes, as shown in a single 10-year follow-up of an infant iron supplementation study in Chile. In that study, 6-month-old infants with high haemoglobin levels (>12.8g/dl) who received iron-fortified formula performed significantly worse ten years later on a battery of neurodevelopmental tasks, and infants with low haemoglobin levels (<10.5g/dl) who received iron-fortified formula performed significantly better (Lozoff et al., 2012). These results emphasize that a nutrient that is beneficial at one dose or time may be toxic at another (Cusick and Georgieff, 2017).

Preclinical studies demonstrate that prenatal **iodine** deficiency results in deficits in neurogenesis, neuronal migration, glutamatergic signalling, and brain weight, and postnatal models affect dendrite-genesis, synaptogenesis, and myelination. Behavioural abnormalities range from global abnormalities in severe deficiency to poorer learning and memory, sensory gating, and increased anxiety in milder deficiency (Navarro et al., 2015).

Annexure 5 elaborates the characteristics of studies on iodine-deficient pregnant mothers and its consequences on their subsequent offspring. Iodine is needed for the formation of thyroid hormones, which are essential for central nervous system development. Pregnant women with severe iodine deficiency may produce less thyroid hormone, leading to cretinism in the child, which is characterized by mental retardation, facial deformities, deaf-mutism, and severely stunted growth (Prado and Dewey, 2014). The developing foetal brain is most susceptible to iodine deficiency during the first trimester when foetal T3 production depends entirely upon the supply of maternal T4. Severe iodine deficiency can result in cretinism, marked by deficits in hearing, speech, and gait and IQ of approximately 30. Iodine supplementation in early pregnancy of women at risk for iodine deficiency results in better cognitive outcomes in offspring (Skeaff, 2011). Low iodine in mothers result in adverse cognitive outcomes in their offspring; low verbal IQ, reading accuracy and reading comprehension (Bath et al., 2013), slower response speed (Finken et al., 2013), reductions of 10% in spelling, 7.6% in grammar, and 5.7% in English-literacy (Hynes et al., 2013). Some studies, however, showed no associations (Zhou et al., 2015; Julvez et al., 2013; Santiago et al., 2013).

Zinc is essential for neurogenesis and migration, myelination, synaptogenesis, regulation of neurotransmitters and signalling in the foetal brain; specifically, the cortex, hippocampus, cerebellum and autonomic nervous system (Cusick and Georgieff, 2017; Vazir and Boindala, 2016). However, the evidence from human studies has not shown positive effects of zinc supplementation during pregnancy or infancy on child cognitive development (Prado and Dewey, 2014). Meta-analyses and reviews of zinc supplementation failed to find a significant effect on child cognition or motor development, likely due to a great degree of heterogeneity in the effect sizes and study designs (Gogia and Sachdev, 2012). Zinc supported sustaining normative neurodevelopment in the first 2 years of life (Colombo et al., 2014). Zinc supplementation improved the rate of head growth in infants in Nepal (Surkan et al., 2012), while it improved alertness and attention

patterns in Indian preterm neonates (Mathur and Agarwal, 2015).

Individual studies reveal key beneficial outcomes when zinc deficiency is prevented in early infancy and the positive impact of zinc when given in combination with iron. On the other hand, a systematic review and meta-analysis did not show the efficacy of zinc with or without iron co-supplementation on child mental and motor development up to 9 years old age (Sajedi et al., 2020). No beneficial effects were seen in the performance in five indicators of information processing (Siegel et al., 2011), motor or mental development (Gogia and Sachdev, 2012) or cognitive improvement in children (Pongcharoen et al., 2011).

One longitudinal Korean study observed that in maternal late pregnancy, **lead** was marginally associated with deficits in mental development index of children at 6 months, especially in mothers having low dietary iron intake during pregnancy (Shah-Kulkarni et al., 2015).

4.2. IMPLICATIONS OF MATERNAL AND CHILD MALNUTRITION ON BRAIN DEVELOPMENT AND FUNCTION

4.2.1. Maternal Malnutrition

Most neurodevelopment is completed during the first 1000 days after conception (Barker, 2012), and optimizing nutrition during this period has become a global priority (Nabarro, 2013). Maternal malnutrition can result in both general and specific neurodevelopmental sequelae. Children of under-weight women have an increased risk of delayed mental development (Hinkle et al., 2012). The hippocampus (memory), the cortex, and auditory development are particularly vulnerable to malnutrition in early pregnancy (Penido et al., 2012). Other effects of early intra-uterine malnutrition only become apparent in later life (Barker, 2012) and include adolescent and adult problems, such as attention-deficit disorder, conduct problems, and eventual low socio-economic status (Galler et al., 2012a; 2012b; 2012c). The inter-generational effect of low SES of parents leads to poor children's growth, poor cognitive development, and the cycle perpetuates.

The developing brain between 24 and 42 weeks of gestation is particularly vulnerable to nutritional insults because of the rapid trajectory of several neurologic processes, including synapse formation and myelination. As the deficiencies affect different parts of the developing brain, different long-term effects would result from varying severities and combinations of deficits (Kerac et al., 2014). In a longitudinal study by Prado et al (2017), maternal supplementation with multiple micronutrients (MMN) showed long-term benefits for child cognitive development (cognitive, motor, and socio-emotional) at 9–12 years of age, thereby supporting its role in early childhood development. At least 16 randomized trials have compared maternal supplementation, showing positive effects of MMN on birth weight and small for gestational age (Ramakrishnan et al., 2012; Kawai et al., 2011), and stillbirths (Haider and Bhutta, 2015). The most recent meta-analyses, including two additional large-scale trials, allay earlier concerns of adverse effects. However, effects on long-term cognitive ability remain equivocal or unknown (Prado et al., 2017).

Basu et al (2017) studied the effect on foetal neural development on full-term, singleton neonates born to mothers with IDA and reported a progressive decline in brain volumes of neonates with increasing severity of maternal anaemia. In contrast, another prospective cohort study (Mireku et al., 2016) conducted on 636 mother-singleton child pairs reported no associations of iron supplementation in iron-deficient mothers on the cognitive and motor development of the infant. Similarly, a review by

Larson et al (2017) also reported that the clinical evidence (11 RCTs) does not show that iron supplementation in pregnancy causes improvements in long-term child mental development.

Bath and colleagues (2013) analyzed mother-child pairs from the Avon Longitudinal Study of Parents and Children cohort by measuring urinary iodine concentration (and creatinine to correct for urine volume) in stored samples from 1040 first-trimester pregnant women. They reported that children of women with an iodine - to - creatinine ratio of <150 µg/g were likely to have scores in the lowest quartile for verbal IQ, reading accuracy, and reading comprehension than were those of mothers with ratios of 150 µg/g or more after adjustment for confounders. Randomized trials of iodine supplementation in pregnant women from regions with severe iodine deficiency confirmed the effect of severe maternal iodine deficiency on children's cognitive development (Zhou et al., 2013).

Choline, a micronutrient found in meat, legumes, and eggs, is needed during pregnancy as it is the seminal source of its metabolites that are used in the development of all tissues, the synthesis of the neurotransmitter acetylcholine, the methylation of genes (epigenetics), and, in general, the one-carbon metabolic pathway. Phosphatidylcholine is a phospholipid that is used in the development of the brain and other tissues and is in high demand during the gestational period (Cheatham, 2019). Clinical trials in humans are few due to ethical concerns. Supplementation with double the recommended amount of choline (930 mg/day) during the third trimester resulted in improved speed of processing in infants (Caudill et al., 2018); supplementation with a lesser amount (750 mg/day) did not improve memory (Cheatham et al., 2012).

There is an increasing interest in the long-term effects of prenatal **folate** deficiency on brain development in the offspring (Benton, 2012; Breimer and Nisson, 2012). Through the epigenetic mechanism of DNA (hypo) methylation, folate deficiency in pregnancy can modify gene expression, causing long-lasting changes in the biological programming of brain development (Nyaradi et al., 2013) for example, folate deficiency in the first trimester may lead to neural tube defects in the foetus. Furthermore, higher maternal folate intake (as measured by an FFQ) in early pregnancy was associated with higher general intelligence in 3 - year - old children (Villamor et al., 2012).

Whitehouse et al (2012) reported a two-fold increase in language impairment in children of mothers with **vitamin D** deficiency (70nmol/L). A positive association between maternal vitamin D concentrations and the child's mental and psychomotor development scores has also been reported (Veena et al., 2016). Another study found higher mental and psychomotor development scores in children of mothers with normal vitamin D status (>75 nmol/L) compared to those with deficiency (<50 nmol/L) (Morales et al., 2012).

4.2.2. Child Malnutrition

Protein Energy Malnutrition (PEM): Early severe protein-energy undernutrition leads to growth restriction. In particular, stunting affects learning and consequent poor cognitive development that may even be irreversible. In India, the prevalence of stunting, wasting and underweight among under 5 children in 2017-2018 was 57.9%, 22.2% and 43.5%, respectively (MoHFW, UNICEF, 2019). Crookston et al (2013) examined the associations between recovery from early stunting and cognitive abilities using longitudinal data from Ethiopia, India, Peru and Vietnam. They found that improving the growth of children who were stunted in infancy and maintaining nutrition in children who might otherwise falter may significantly benefit their schooling and cognitive achievement.

A growing body of evidence from cross-sectional and prospective studies has shown that stunting, an indicator of chronic malnutrition, is associated with reduced cognitive and motor development

(Sudfeld et al., 2015a). In contrast, there is limited evidence regarding the independent association between wasting, an indicator of acute malnutrition, and child development. Despite the large volume of literature linking malnutrition to developmental deficits, there is comparatively limited evidence on the association between known risk factors for malnutrition and child development (Black et al., 2013). A study by Sudfeld et al (2015b) on 1036 Tanzanian children, 18 to 36 months of age, reported that both stunting and wasting were significantly associated with poor cognitive-developmental scores, thus corroborating a large base of observational evidence that links chronic malnutrition with cognitive and developmental motor deficits (Sudfeld et al., 2015a). Evidence from low and middle-income countries suggests that the prenatal period (Christian et al., 2014) and the first 24 months after birth (Manji et al., 2015; Hamadani et al., 2014; Black et al., 2013) are the most sensitive times for stunting to be associated with later cognition, executive function, and school attainment. After 24 months the association is not as strong (Hamadani et al., 2014). Some catch up is possible in height-for-age after 24 months, with uncertain cognitive gains (Casale and Desmond, 2016; Crookston et al., 2013). Early-onset persistent stunting was associated with lower cognitive development in 5 year old children in the MAL-ED cohort study who were followed from birth to 5 years of age in six LMICs, including India (Alam et al., 2020).

Iron Deficiency: During prenatal and neonatal periods, iron deficiency can alter myelination, monoamine neurotransmitter synthesis, and hippocampal energy metabolism. Assessment of these effects utilizes tests for speed of processing (myelination), changes in motor and emotional affect (monoamines), and recognition memory (hippocampus). Infants and young children with IDA are at risk of developmental difficulties involving cognitive, social-emotional, and adaptive functions (Bener et al., 2014). Other studies have documented delays in both language and motor development. Breastfeeding is usually protective, but not if the mother is iron deficient. Therefore, careful monitoring and adequate supplementation are needed for at-risk infants (Abu-Ouf and Jan, 2015). Systematic reviews have summarized the impact of iron supplementation on child cognitive development through meta-analysis. Pasricha et al (2013) meta-analyzed the effects of daily iron supplementation in children 4–23 months of age and found no clear evidence of benefit from iron on cognitive development at the end of the intervention even among those who had been anaemic at baseline.

Children, 2-5 year old, receiving iron supplementation had higher hemoglobin greater than and ferritin than controls. Limited evidence suggested that iron supplementation produced a small improvement in cognitive development but had no effect on physical growth There is a concerning lack of data on the effect of iron supplementation on clinically important outcomes including anemia, ID anemia, ID, and cognitive development. Additional interventional studies in this age group are needed (Thompson et al., 2013). Wang et al (2013) undertook a Cochrane review to assess the effects of iron supplementation on cognitive development in iron-deficient anaemic children under 3 years and did not find evidence that iron supplementation improved cognitive development in this group. Scott and colleagues (2018) evaluated the effect of iron-biofortified pearl millet for 6 months on cognitive performance in Indian school-going adolescents. They reported that the intervention improved attention and memory in adolescents in comparison to the conventional pearl millet. They also noted that reaction time decreased twice as much in those consuming biofortified pearl millet on attention tasks (Scott et al., 2018).

4.3. DIETARY PATTERNS AND FOOD GROUPS

Nutritional components, as well as diet as a composite, affects brain maintenance and function. Healthy dietary patterns may protect against dementia and mild cognitive impairment. Furthermore, Smyth et al (2015) report that higher diet quality in terms of a higher intake of healthy food choices is a powerful potential method for lowering the global burden of cognitive decline. Wright et al (2017) show that higher diet quality is associated with better performance, especially in verbal retention and memory, irrespective of race and poverty status. There is evidence to support the 'whole diet approach' theory i.e. a balanced diet, as a whole, rather than single nutrients is beneficial for brain health. Specific dietary patterns that may prove more valuable than consuming individual food/food groups include the Mediterranean diet, the Nordic Diet and the DASH Diet.

The Mediterranean Diet refers to the diet of people residing in Greece, Spain, France, Italy as well as Egypt, Algeria, Libya. The key features of this diet is consumption of unrefined carbohydrates and starches are consumed in large amounts along with cheese, yoghurt, fruits and vegetables. Chicken, fish and eggs are consumed a few times a week, while red meats are not consumed more than a few times in a month. Fat content varies from 28 to 40 %, mainly from an unsaturated source, olive oil (Aridi et al., 2017). Studies have shown that this diet is linked to a low risk of cognitive decline (Kesse-Guyot et al., 2013; Samieri et al., 2013; Lourida et al., 2013), lower prevalence of dementia, depression, (Solfrizzi and Panza, 2014; Woodside et al., 2014; Chao et al., 2014; Matthews et al., 2013; Norton et al., 2013) and reduced risk of Alzheimer's disease (Lourida et al., 2013). In a PREDIMED sub-study (Valls-Pedret et al., 2015), cognitive performance was assessed at baseline and after a median follow-up of over four years. There was cognitive improvement in participants allocated the Mediterranean diet and cognitive decline in those assigned the control diet.

The Nordic Diet is based on the types of food consumed in Scandinavian countries (Morris, 2016). The emphasis is on non-animal based nutrients such as fruits and vegetables and the consumption of fish, canola oil, and several types of meat. A 4-year study on 1,140 men and women with normal cognition to examine the associations of the Nordic Diet with cognitive function showed that subjects who followed the guidelines of the Nordic Diet had increased levels of cognitive functioning compared to baseline (Männikkö et al., 2015).

The DASH (Dietary Approaches to Stop Hypertension) Diet is characterized by a low sodium intake and small portion sizes, which have substantial health benefits. The DASH diet improved cardiovascular risk factors and had greater beneficial effects in subjects with an increased cardiometabolic risk (Siervo et al., 2014). MIND or Mediterranean-DASH (Dietary Approaches to Stop Hypertension) Intervention for Neurodegenerative Delay includes specific guidelines beneficial for brain health. More research is needed to establish the role of this diet in maintaining brain health. The foods included in the MIND diet are antioxidant-rich to enhance cognition; green leafy vegetables to prevent cognitive decline (Morris et al., 2018), blueberries to improve memory (Boespflug et al., 2018; Nilsson et al., 2017; Whyte et al., 2016),fish helps maintain cognitive function due to high amounts of EPA and DHA (Ghasemi et al., 2018).

Evidence strongly suggests that Asian plant-based dietary patterns based on foods like

green leafy and other vegetables, soy, whole grains, green tea, mushrooms, and seaweed is associated with reduced risk of cognitive impairment, slower rate of cognitive decline, better scores on logical memory, or higher global cognitive assessment scores (Rajaram et al, 2019).

4.3.1. Importance of Breakfast

Literature has addressed the effects of consuming breakfast on cognition. Breakfast composition has a profound impact on multiple cognitive domains: attentional capacity (An et al., 2015); processing speed (Jones et al., 2012); working memory (Owen et al., 2012); immediate recall, delayed recall, recognition (Sünram-Lea et al., 2011). Adolphus and colleagues (2016) report in their review that breakfast consumption in children and adolescents (4-18 years), relative to fasting, had a short-term (same morning) positive domain-specific effect on cognition tasks requiring attention, executive function, and memory. In adults aged over 18 years, breakfast consumption showed a small but robust advantage for memory (particularly delayed recall). Largely equivocal results emerge for attention and motor and executive function. There were no effects from breakfast on language (Galioto et al., 2016).

4.3.2. Food Group Intake

The role of different food groups on brain function and cognitive decline has been documented. Consumption of refined cereals and grains were associated with worse cognitive function and decline (Shakersain et al., 2018), while unrefined cereals and whole-grain consumption was associated with better cognitive function (Anastasiou et al., 2017; Samieri et al., 2013b; Wengreen et al., 2013). An inverse relationship has been observed between refined carbohydrate consumption and non-verbal intelligence (Abargouei et al., 2011). A positive association was noted between fish intake and cognition as seen in both cross-sectional and longitudinal studies (Bhushan et al., 2018; Shakersain et al., 2018; Bajerska et al., 2014; Valls-Pedret et al., 2012). Fish consumption lowered the risk of cognitive decline, mild cognitive impairment (MCI) and dementia (Bhushan et al., 2018; Shakersain et al., 2018; Anastasiou et al., 2017; Bajerska et al., 2014). One study reported better attention, visual memory, episodic verbal memory, working memory and executive function in adults and elderly who consumed fish but worse cognitive and executive function was reported in subjects on the consumption of red meat (Bajerska et al., 2014). Dairy consumption (high-fat milk) was associated with worse cognitive function (Bajerska et al., 2014) and cognitive decline (Shakersain et al., 2018), while no association was seen with cheese (Hosking et al., 2019) and ice-cream intake (Shakersain et al., 2018). In addition, single foods, such as avocados (Scott et al., 2017), berries (Whyte et al., 2018), or extra-virgin olive oil (Klimova et al., 2019) are connected with the delay of cognitive decline (Klimova et al., 2020). Details of these studies are given in ***Annexure 6.***

Better cognitive function and less cognitive decline were seen in subjects who consumed plant-based foods (Bhushan et al., 2018; Trichopoulou et al., 2015; Bajerska et al., 2014; Samieri et al., 2013a), olive oil (Galbete et al., 2015; Bajerska et al., 2014; Valls-Pedret et al., 2012), legumes (Wengreen et al., 2013) and walnuts (Hosking et al., 2019; Bhushan et al., 2018; Wengreen et al., 2013) in cross-sectional as well as longitudinal studies. Green leafy vegetable consumption did not lower the risk of cognitive impairment (Hosking et al., 2019). Fruits, berries, potatoes and vegetable consumption were not associated with better cognitive function (Hosking et al., 2019; Anastasiou et al., 2017; Bajerska et al., 2014; Titova et al., 2013; Valls-Pedret et al., 2012). The effects of a plant-based diet reviewed by

Medawar et al (2019) reported the effects on cognition/cognitive processes, brain activity for language and empathy-related tasks, emotional health, and personality traits. Rajaram and others (2019) also reported that citrus fruits, grapes, berries, cocoa, nuts, green tea and coffee improved specific cognitive domains, especially the executive functions. However, they established no causal relationship between the use of a plant-based diet and its putative effects on cognitive functions, mental and neurological functions. Khan et al (2015) also demonstrated that children's diet quality, specifically dietary fibre, is an important correlate of performance on a cognitive task needing variable amounts of cognitive control. Participants in the Mediterranean diet plus nuts group had improvement in the memory composite compared with those ascribed the control diet (Valls-Pedret et al., 2015). Two observational studies, the Doetinchem Cohort (Nooyens et al., 2011) and the Nurses' Health Study (O'Brien et al., 2014), reported that long-term nut consumption was related to overall cognition at an older age but not to cognitive decline during follow-up for 5 to 6 years. ***Annexure 7*** gives details of such studies.

Alcohol intake was not associated with cognitive function (Bhushan et al., 2018; Tanaka et al., 2018; Anastasiou et al., 2017; Qin et al., 2015; Bajerska et al., 2014), except better global cognition was associated with wine intake in community-dwelling residents of Spain (Valls-Pedret et al., 2012). No association with cognitive decline was seen with intake of spirits/beers in the longitudinal study by Shakersain et al (2018). ***Annexure 8*** shows that no association with cognitive decline or impairment was observed in longitudinal studies conducted on the intake of sugar/fruit juices (Shakersain et al., 2018), sweetened beverages, and sodium intake (Wengreen et al., 2013), processed and fast/fried food, and sweets and pastries (Hosking et al., 2019), animal-source cooking fat (Qin et al., 2015). Cohen and others (2018) reported that sugar consumption, especially from sugar-sweetened beverages, during pregnancy and childhood, and maternal diet soda consumption may adversely impact child cognition. In contrast, fruit consumption by children may lead to improvements.

A systematic review to evaluate the impact of healthy diet consumption among children and adolescents on executive functioning reported that among the ten studies examining foods, there was a positive association between healthier foods (e.g. whole grains, fish, fruits and/or vegetables) and executive function (Cohen et al., 2016). In contrast, less-healthy snack foods, sugar-sweetened beverages and red/processed meats were inversely associated with executive functioning.

Certain herbs that may prove beneficial in enhancing cognition or delaying cognitive decline include ashwagandha, turmeric, brahmi etc.. In a systematic review (Ng et al., 2019), the extract of *Ashwagandha (Indian Ginseng/ Winter Cherry)* corrected mild cognitive impairment and enhanced executive functions in adults with MCI. Curcumin present in *turmeric* reduces oxidative damage and improves cognitive functions related to senescence. It also binds with β-amyloid plaques and inhibits its aggregation and is beneficial in Alzheimer's disease. An RCT demonstrated that 400 mg/day of curcumin improved performance on sustained attention and working memory tasks in elderly over 60 years of age (Cox et al., 2015). *Brahmi* is commonly used as a memory enhancer.

4.3.3. Other Dietary Components

Polyphenols are secondary metabolites of plants and comprise flavonoids, lignans, stilbenes, coumarins and tannins. They are present abundantly in colourful fruits (berries, grapes, tomatoes), vegetables, tea, spices, herbs

and olive oil. They contribute towards brain health similar to antioxidants by regulating oxidative stress and mediating anti-inflammatory mechanisms (Cherniack, 2012). The extensively studied group in relation to brain health, under polyphenols, are flavonoids. Studies have shown associations between flavonoids and delayed cognitive decline (Schaffer and Halliwell, 2012) and enhanced language and verbal memory tasks (Kesse-Guyot et al., 2012). Cocoa flavonoids (in dark chocolate), enhance cognition (Mastroiacovo et al., 2015; Brickman et al., 2014); however, the study performed on participants with cognitive impairment involving cocoa flavonoids was inconclusive (Mintzer et al., 2019). An RCT conducted on healthy adults aged 50-69 years reported that a high cocoa flavanol containing diet enhanced gyrus function after 3 months (Brickman et al., 2014) and was associated with 41% lower risk of cognitive decline (Moreira et al., 2016).

In the review by Jirout et al (2019), greater levels of **carotenoids** found in leafy vegetables, were associated with higher scores on cognitive tests in the visual-spatial domain (Saint et al., 2018). Lutein, one of the three major types of dietary carotenoids, is present in the brain (Mulder et al., 2014), and has “functional importance” on cognition and infant brain development. Interestingly, lutein concentration was higher in brains of children than adults and was specifically related to cognition, i.e. measures of executive function, language, learning, and memory (Jia et al., 2017) and improved the speed of temporal processing in young adults ((Lieblein-Boff et al., 2015). It is also associated with macular pigment density, which interacts with cognitive functioning (Jia et al., 2017).

There are limited studies to elucidate the role of **caffeine** in memory and cognition enhancement. High serum levels of caffeine delayed dementia progression in a case-control study on 124 older persons with MCI (Cao et al., 2012). However, another study did not find an association with risk of cognitive impairment, overall dementia or AD (Gelber et al., 2011). A longitudinal study reported less cognitive decline among coffee consumers but no dose-response (Arab et al., 2011).

Soy isoflavones include genistein and daidzein, and their effects on cognition are variable and inconclusive (Soni et al., 2014) with an overall absence of adverse events (Alekel et al., 2015). An initial positive cognitive effect in adult age appears to reverse in older women; in men, the data are even more equivocal (Soni et al., 2014).

In the Doetinchem Cohort Study, including 2613 participants aged 43-70 years, higher consumption of **allium** (onion, garlic, and leek) was associated with worse scores on cognitive flexibility and speed of cognitive processes in cross-sectional analyses, while in longitudinal studies, allium consumption was not associated with cognitive decline (Nooyens et al., 2011).

4.4. MICROBIOME - GUT - BRAIN AXIS

The concept of the microbiome-gut-brain axis has emerged in recent years. The bidirectional interaction between the gut and the brain is now well recognized. Emerging evidence has suggested the importance of the gut microbiome in this two way communication system (enabling the gut microbes to communicate with the brain and the brain with the gut) (Keunen et al., 2015).

The term "gut microbiome" refers to the complex ecosystem of bacteria that colonize the gut, including their genes, proteins, and metabolites (Korecka and Arulampalam, 2012). Although research has not addressed how the gut microbiome may modulate brain development, immune signalling is likely to play a crucial role (Keunen et al., 2015). The benefits of human-microbe symbiosis is now known to extend to

human mental health, with growing evidence that the gut-brain axis plays a crucial role in maintaining brain health via bidirectional communication between the microbes and brain (Mohajeri et al., 2018; Mayer et al., 2014). It also influences human behaviour and is known to affect the pathophysiology of mental illnesses (Mohajeri et al., 2018; Foster & McVey Neufeld, 2013).

Immune cells, cytokines, and chemokines are the microbiome's mechanisms to interact with the brain. In addition, many immune-related signalling molecules regulate processes in the brain and vice versa (Keunen et al., 2015; El Aidy et al., 2014).

The gut microbiota may modulate brain function and development through immune signalling (e.g., pro-and anti-inflammatory cytokines, chemokines, and immune cells), endocrine and neural pathways. Conversely, the brain may exert the influence on the gut through neurotransmitters that impact immune function and alter cortisol levels, intestinal motility, and permeability. Nutritional components may influence each of these communication pathways (Keunen et al., 2015). Microbiota dynamically changes across the lifespan, establishing their relationship with the host at critical windows during infancy, adolescence and ageing. At these time windows, there is an increased vulnerability to external insults, resulting in enhanced susceptibility to brain disorders. Early life disturbance of the developing gut microbiota can impact neurodevelopment significantly and lead to adverse mental health outcomes later in life.

Similarly, the microbiota may contribute to the ageing process and the trajectory of neurodegenerative disorders (Dinan & Cryan, 2017). The gut microbiota also regulates key central neurotransmitters by altering levels of precursors; the inhibitory neurotransmitter γ-aminobutyric acid is produced by *Lactobacillus* and *Bifidobacterium* species; *Escherichia*, *Bacillus* and *Saccharomyces* spp can produce noradrenaline (norepinephrine). On the other hand, *Candida*, *Streptococcus*, *Escherichia* and *Enterococcus* spp. produce serotonin, and *Bacillus* can produce dopamine, whereas certain *Lactobacillus* spp. can produce acetylcholine (Dinan & Cryan, 2017; Wall et al., 2014). These microbially synthesized neurotransmitters can cross the mucosal layer of the intestines and possibly mediate physiological events in the brain (Dinan & Cryan, 2017). Short-chain fatty acids, including propionate, butyrate and acetate, are important metabolic products of gut microbial activity and may exert central effects directly or indirectly (Dinan & Cryan, 2017; Stilling et al., 2016; Paul et al., 2015).

The chance of providing cognitive support to humans may be greatest during gestation, infancy, and older age (Prenderville et al., 2015), as these are periods of life with the highest vulnerability and the greatest demand for nutrients. To date, the majority of mechanistic evidence for the involvement of the gut microbiota in cognition is provided by animal experiments of induced infections (Gareau et al., 2014; 2011), antibiotic and dietary manipulations (Frohlich et al., 2016; Desbonnet et al., 2015; Ohland et al., 2013) and probiotic interventions (Davari et al., 2013; Ohland et al., 2013).

Several studies have reported improvements in cognitive function on administration of probiotics, paarticulary in those with MCI (Chung et al., 2014; Akbari et al 2016; Hwang et al., 2019; Coutts et al., 2020). However, Louzada et al (2020) reported no effect on cognition on administration of a synbiotic.

5. COGNITIVE DECLINE WITH AGE AND DEMENTIA

Advancing age results in cognitive decline which is associated with a deterioration in specific cognitive abilities, like processing speed, language, memory, and executive functioning abilities.

Different cognitive domains have strikingly different trajectories. A linear decline is not the norm, and a more complex quadratic pattern frequently occurs with a period of stability or mild decline followed by an accelerated decline one or two years before diagnosis.

Diet, physical activity and social factors are the major modifiable risk factors for cognitive decline with age.

Interventions cannot change non-modifiable risk factors such as age, sex, race/ethnicity, and family history. However, these are relevant to intervention effectiveness because they can modify the effect of interventions.

Between the years 2015 and 2050, 22% of the global population will be over the age of 60; the number of people aged 65 or older will outnumber children under the age of five (WHO, 2018). Indian elderly population aged 60 years and older has increased from 5.5% in 1950 to 10.1% in 2021 and is further expected to increase to 19.5% by 2050. In absolute numbers, there were 103 million elderly persons of age 60 years and above in 2011 (as per the 2011 census). According to the UN Population Division, this figure will increase to 319 million by 2050 (UN, 2019). The projected increase in ageing persons will place significant additional pressure on the individual, family, societal, and economic resources (Kremen et al., 2012). Advancing age results in cognitive decline that is associated with deterioration in certain cognitive abilities, such as processing speed, language, memory, and executive functioning abilities (Harada et al., 2013).

5.1. PATTERNS OF COGNITIVE DECLINE

Some subtle decline in cognition associated with ageing is considered normal or inevitable, particularly for people over 60 years of age. Reaction time and speed of processing decline slowly throughout adulthood. Therefore, greater difficulty in learning new information by 70 or 80 years old may not be a warning of neurocognitive disease in the absence of other signs or symptoms of cognitive difficulty (Kane et al., 2017). If the extent of decline crosses a threshold (variously defined), the individual is said to have some intermediate form of cognitive impairment. One way of determining this threshold is when the decline in cognition is recognized by an individual, caregiver, or health professional and requires the individual to compensate using tools such as lists or maps to continue to perform daily activities (Kane et al., 2017). Cognitive change as a normal process of ageing is well documented in literature. Some cognitive abilities, such as vocabulary, are resilient to brain ageing and may even improve with age. Other abilities such as conceptual reasoning, memory, and processing speed decline gradually. There is significant heterogeneity among older persons in the rate of decline in some abilities, such as perceptual reasoning and processing speed (Harada et al., 2014; Wisdom et al., 2012).

5.1.1. Cognitive Severity Stages (Normal Ageing to Dementia)

The four cognitive stages spanning from normal ageing to dementia are:

a) ***No Cognitive Impairment (NCI)*:** No decline in cognition or complex skills relying on their cognitive abilities. This stage includes normally ageing adults and those with a cognitively impairing disorder that is not severe enough to produce any change in their abilities. The average duration is 30 years.

b) ***Subjective Cognitive Impairment (SCI)*:** A perceived or subjective decline in cognitive or functional abilities that does not affect performance of the usual or most complex activities. This stage also characterizes normal ageing older adults and those who are becoming progressively more impaired due to a cognitive disorder. In AD, this stage lasts 15 years.

c) ***Mild Cognitive Impairment (MCI)*:** Decline in cognitive abilities that is not due to normal ageing such as in language, memory reasoning, judgment, or perception. Individuals with MCI can independently perform daily survival tasks like drive, pay bills, manage finances, do household chores and other skills that do not require learning new information. MCI is not seen in normal ageing and is due to one or more cognitive disorders. In AD, MCI lasts an average of 7 years.

d) ***Dementia*:** This is the level of severity after the MCI stage in most cognitively impairing disorders. Individuals in the dementia stage have deteriorated in the ability to perform instrumental activities of daily living (IADL), which includes well-learned skills such as cooking, shopping, driving, doing housework, performing well-learned hobbies. The dementia progresses to affect more well-learned skills, called basic activities of daily living, including bathing, dressing, toileting. It finally progresses to affect walking, speech, swallowing and even control of the trunk, neck and face. Dementia is not seen in normal ageing individuals and is due to one or more cognitive disorders. In AD, the dementia stage lasts an average of 7 years (Hoag, 2021).

5.2. DEMENTIA

Dementia is a syndrome, usually of chronic or progressive nature, in which there is deterioration in cognitive function beyond normal ageing. Dementia affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. However, consciousness is not affected. The cognitive impairment is commonly accompanied and occasionally preceded by deterioration in emotional control, social behaviour, or motivation (WHO, 2020). Dementia results from diseases or injuries that primarily or secondarily affect the brain, such as Alzheimer's disease or stroke. Dementia is one of the salient causes of disability and dependency among older persons. The impact of dementia on the carers, family, and the society can be physical, psychological, social, and economic (WHO, 2020).

5.2.1. Signs and Symptoms of Dementia

Dementia may affect each person differently, depending upon the effect of the disease and the person's personality before becoming ill. The signs and symptoms are categorized in three stages.

The early stage of dementia is often overlooked because the onset is gradual. Common symptoms include forgetfulness, losing track of time, becoming lost even in familiar places. Progression to the middle stage results in the signs and symptoms like forgetting names, becoming lost at home, experiencing behaviour changes become more apparent and restrictive. The late stage of dementia is one of near-total dependence and inactivity. Symptoms include losing awareness of time and place, having difficulty recognizing relatives and friends, increasing need for assisted self-care, difficulty walking, and experiencing behaviour changes that may escalate and include aggression (WHO, 2020).

5.2.2. Alzheimer's Disease

Alzheimer's disease (AD), acknowledged as a progressive multifarious neurodegenerative disorder, is the leading cause of dementia. It is characterized by intracellular neurofibrillary tangles and extracellular amyloidal protein deposits which contribute to senile plaques. While the neuropathological features of AD are recognized, the intricacies of the mechanism are not clearly established. AD is an irreversible, progressive brain disease that slowly destroys memory, language, thinking skills and the ability to plan. Over time, the ability to carry out even simple tasks of daily living is lost. In most people with AD, symptoms appear after 60 years, though younger ages are also affected (BUMC, 2013).

5.3. RISK FACTORS FOR COGNITIVE DECLINE / IMPAIRMENT AND ALZHEIMER'S DISEASE

5.3.1. Genetic Factor

AD can be classified based on the age of onset of the initial symptoms. Early-onset AD affects persons under 65 years of age, accounting for about 4–6% of the cases, while the late form AD affects individuals aged 65 years or older. According to Ballard et al (2011), about 70% of the AD risk can be attributed to genetics. Early AD usually occurs due to gene mutations in the amyloid precursor protein, presenilin 1 and presenilin 2, whereas late AD is associated with polymorphism in APOE gene (apolipoprotein E gene), especially the presence of ε4 allele (Ravindranath and Sundarakumar, 2021; Cacace et al., 2016; Calero et al., 2015).

5.3.2. Acquired Risk Factors

Several external factors increase the risk of developing AD. Among those factors are cerebrovascular diseases, diabetes, hypertension, obesity and dyslipidemia. The association of the risk factors to AD development as well as some protective factors such as cognitive reserve, physical activity and diet (Mayeux and Stern (2012) are described in the following subsections.

Obesity: In AD development, the role of obesity as a risk factor is unclear, with studies presenting heterogeneous results. Weight loss at advanced ages occurs in relation to other comorbidities and often indicates poor health and may even precede onset of dementia within 10 years (Silva et al., 2019). A meta-analysis by Anstey et al (2011) indicated that low weight and overweight and obesity in middle-age are associated with a higher risk of developing AD in late life.

Cardiovascular Health: in their review article, Qiu and Fratiglioni (2015) have reported a significant role of cardiovascular burden in age-related cognitive decline. Cognitive decline and CVDs share many vascular risk factors like smoking, hypertension, and diabetes mellitus; CVDs can cause cerebral hypoperfusion, hypoxia, emboli, or infarcts, thus contribute to cognitive decline. Heart disease results in a reduction in cerebral perfusion, causing damage to nerve cells (Kwok et al., 2011), brain dysfunction, and decline in cognition (Alosco et al., 2013). Cardiovascular diseases induce a lack

of oxygenation in the brain, leading to cognitive impairment and dementia mediated by an increase in Aβ levels. Although preexisting Aβ aggregates can also induce cerebral perfusion impairment, a history of hypertension, stroke, or heart disease is a risk factor to develop AD (Edwards et al., 2019).

Cerebrovascular Diseases: Risk factors for cerebrovascular diseases and AD often overlap. Cerebrovascular changes such as haemorrhagic infarcts, small and large ischemic cortical infarcts, vasculopathies, and changes in cerebral white matter increase the risk of dementia (Silva et al., 2019).

Dyslipidemia: Elevated cholesterol levels are risk factors for the development of AD. Studies have demonstrated 10% higher cholesterol levels in patients with AD than healthy individuals (Popp et al., 2013). High serum cholesterol levels are linked to elevated Aβ levels and more cognitive impairment and progression in AD. Cholesterol impairs Aβ degradation and promotes its production (Barbero-Camps et al., 2018).

Type-2 Diabetes Mellitus: Epidemiological studies indicate a definite association between type 2 diabetes mellitus and the increased risk of developing AD. Several mechanisms are suggested, including insulin resistance and insulin deficiency, impaired insulin receptors, toxicity of hyperglycemia, deleterious effects due to advanced glycation end products, cerebrovascular damage, vascular inflammation and others (Li et al., 2015).

Traumatic Brain Injury: Recent research has reiterated that traumatic brain injury (TBI) is a vital factor that leads to the advancement of AD or dementia. After a TBI event, dementia diagnosis was most robust within the first year (4–6 times) but maintained significance for up to 30 years (Nordström and Nordström, 2018). In a large cohort study, overall risk of dementia was 24% higher in individuals with a history of TBI than those without a history of TBI.

Epilepsy: Epilepsy is defined as a neurological disorder with a continual and spontaneous propensity to seizures, as convulsions or non-convulsions, due to abnormal neural firing and networks (Edwards et al., 2019). The imbalances in functional neuronal network in epilepsy can result in neuropathological changes, brain atrophy, and cognitive decline (Friedman et al., 2012). MCI and early-stage AD patients with epilepsy show an earlier onset of AD and rapid decline in cognition (Vossel et al., 2013, 2016; Cretin et al., 2016). Multiple studies also indicate that AD patients have a greater risk of developing seizures or epilepsy (Vossel et al., 2016). Additional studies post that younger age of dementia onset is correlated to increased seizure risk (Horvath et al., 2016). Seizures are common in cases of familial AD and are related to cases of Down syndrome. Thus, epileptic seizures could be an early manifestation in AD progression or a constituent of AD severity. However, more research is needed, as a systemic meta-analysis between dementia and epilepsy concluded significant knowledge gaps in epidemiology between the two disorders with insufficient data to pool an overall incidence rate (Edwards et al., 2019).

5.3.3. Lifestyle

Physical Activity: Usually, an elderly individual without dementia will exhibit hippocampal volume shrinkage of 1-2 % each year which may be reversed by moderate-intensity exercise (Erickson et al., 2011). Individuals with a life-long exercise routine reveal larger brain volume and improved executive function than inactive older adults (Tseng et al., 2013). There is evidence indicating that physical exercise has a beneficial effect on

cognitive performance and the rate of cognitive ageing.

While the weight of evidence suggests benefits from aerobic exercise, further research into the effect of resistance or combined exercise on these mechanisms and cognition is warranted (Kennedy et al., 2017). The intensity and duration of exercise also have a dose effect on both the mechanisms and positive cognitive outcomes; the evidence for this dose-response is not comprehensive. In addition, the mechanisms reviewed do not exist in isolation, with each one affecting the other to some degree (e.g., Marosi and Mattson, 2014; Ghasemi et al., 2013). Examination of these relationships in future research is highly recommended to develop a more comprehensive understanding of the relationship between exercise and cognitive ageing (Kennedy et al., 2017).

Yoga: Yoga combines physical activity as postures with yoga-based meditative and breathing exercises. The findings from studies suggest that yoga confers similar cortical neuroprotective effects as physical activity (Gothe et al., 2019). There is some evidence that yoga-induced improvements in sleep mediate the effects of yoga on cognition (Brenes et al., 2018; Janelsins et al., 2016). Similarly, yoga improves mood and neuropsychiatric symptoms in cognitively impaired adults, thereby preventing deterioration in patients' ADLs and cognitive performance (Brenes et al., 2018).

Gothe and colleagues (2019) narrate that yoga practice is linked to anatomical changes in the frontal cortex, hippocampus (related to learning and memory processes), anterior cingulate cortex (related to cognitive operations including stimulus processing and memory updating) and insula. Yoga practice showed a positive relationship with measures of brain structure (i.e. grey matter volume and density, cortical thickness). Lowering stress and cortisol through yoga may also impact hippocampal function/structure (Brenes et al., 2018).

Diet: Large observational studies (Singh et al., 2014; Lourida et al., 2013; Psaltopoulou et al., 2013) provide longitudinal evidence of a moderate protective effect of the Mediterranean diet against cognitive decline and Alzheimer disease. Another systematic review (van de Rest et al., 2015) reported that better adherence to a Mediterranean diet is associated with lesser cognitive decline, dementia, or Alzheimer disease, as evident in several cross-sectional , longitudinal studies, trials and meta-analyses. Other healthy dietary patterns, derived both a priori (e.g., Healthy Diet Indicator, Healthy Eating Index, and Program National Nutrition Santé guideline score) and a posteriori (e.g., factor analysis, cluster analysis, and reduced rank regression), were associated with reduced cognitive decline and/or a reduced risk of dementia as shown by all 6 cross-sectional studies and 6 of 8 longitudinal studies. A detailed description of the role of diet and its constituents, nutrients and their deficiencies on cognitive decline is given in Chapter 4.

Smoking: Smoking may influence the risk of developing AD by various mechanisms. It can raise the generation of free radicals, increase oxidative stress, and promotes inflammation in the immune system, resulting in the activation of phagocytes and additional oxidative damage. Moreover, smoking may lead to cerebrovascular diseases, which increase the risk of AD (Durazzo et al., 2014). According to Durazzo et al (2014), the evidence in the literature is enough for smoking cessation to be recommended to reduce the incidence of dementia.

Alcohol: Alcohol affects cognitive and motor functions negatively; hence, heavy drinking is associated with an increased risk of AD. Mild to moderate alcohol intake is associated with a lower

AD risk (Heymann et al., 2016). Loss of cholinergic neurons seen in AD patients is also reported in individuals consuming ethanol (Vetreno et al., 2018; Fernandez and Savage, 2017). Both smoking and drinking together can have a stronger effect on AD incidence than just one of them (Zhou et al., 2014). Some recent reports state that alcohol is not associated with AD or its progression (Heffernan et al., 2016; Bos et al., 2017). Abstaining from alcohol after AD diagnosis seems to ameliorate the cognitive damage initially observed (Toda et al., 2013). This suggests that alcohol consumption can increase the risk of AD and worsen the progression of the disease under heavy intake conditions (Heymann et al., 2016).

Meditation: Meditation increases regional cerebral blood flow in the brain's frontal and anterior cingulate regions, efficiency in the brain's executive attentional network, and electroencephalogram (EEG) coherence. A study on the effect of meditation on the executive attentional network found that meditators were faster on all tasks. With ageing, the brain cortical thickness (grey matter, which contains neurons) decreases, whereas meditation experience is associated with an increase in grey matter in the brain (Sharma, 2015) as well as more folds in the brain's outer layer (Luders et al., 2012). This process, known as gyrification, may increase the brain's ability to process information. Desbordes and colleagues (2012) observed that meditation can affect activity in the amygdala and that different types of meditation may affect the amygdala differently even when the person is not doing meditation.

Cognitive Reserve and Cognitive Training: MacKinnon-Lee and Bahr (2020) described the evidence that higher socioeconomic status, bi- or multilingualism, education levels, IQ, occupational complexity, relationships like marriage vs living alone and social networks can buffer and delay cognitive ageing thus contributing to higher cognitive reserve (Elovainio et al., 2018; Mazzuco et al., 2017; Yates et al., 2017). It is suggested that women have more positive exchanges with children, family members, and friends than men. These positive exchanges may indicate greater cognitive stimulation for women than men (Stafford et al., 2011). A review analyzing RCTs of mental engagement/cognitive training interventions showed improvements in immediate and delayed recall among the intervention group compared with the control group (Martin et al., 2011). However, no data exists on which engagement/activity is the most beneficial (Baumgart et al., 2015). Activities / games associated with brain health are:

- Computer use, craft activities, social activities, and playing memory games (Krell-Roesch et al., 2019).
- Crossword puzzles and jigsaw puzzles delay memory decline and was associated with perception, mental rotation, working memory, reasoning and global visuo-spatial cognition (Fissler et al., 2018; Pillai et al., 2011).
- Sudoku (number-puzzle) played more than once a day leads to superior cognitive performance (Brooker et al., 2018).
- Chess and other cognitive leisure activities improve memory, executive functioning and processing speed (Lane and Chang, 2018; Fattahi et al., 2016) and also help protect against dementia (Lillo-Crespo et al., 2019).
- Checkers improved markers of cognitive health in people at risk of Alzheimer's disease (Schultz et al., 2015).
- Video games (action, puzzle and strategy games) improve attention, problem-solving and cognitive flexibility (Green and Seitz, 2015).
- Learning new skills such as quilting or photography or a musical instrument (Balbag et al., 2014) enhanced memory function (Park et al., 2014). Learning new language and

improving vocabulary may play a role in delaying the onset of Alzheimer's disease and other forms of dementia (Kim et al., 2019) .

5.3.4 . Social Factor

Old age, sex, marital status, education, socioeconomic position, and social isolation are also associated with cognitive decline (Lee et al., 2012). A study by Lee and Kim (2016) found that older adults who participated more frequently in senior citizen clubs or senior centres at baseline had a lower risk of cognitive decline 4 years later than those who did not. A possible reason for this is that senior centre participants are more involved in cognitively and emotionally stimulating activities than non-participants.

Chanda and Mishra (2019) conducted a secondary analysis using data from WHO's Study on Global Ageing and Adult Health (WHO-SAGE, Wave1) to understand the patterns of cognitive decline among the elderly through proximate and dynamic factors. They reported that the higher the social participation, the better was the mean cognitive scores among the elderly. Retirement accompanied with 'more' social participation is beneficial for maintaining cognitive health in the later years of life (Chanda and Mishra, 2019).

Frequent contact with children by telephone or letters was associated with reduced risk of cognitive decline 4 years later in old-old adults, as reported in a study from Korea. This finding agrees with previous study results reporting that frequent contact with children on phone or through letters was significantly protective against depression among older people (Lee and Kim, 2014).

5.3.5. Other Risk Factors

Formal Education: A study reported how early cognitive symptoms might emerge preceding Alzheimer's dementia, particularly in higher-educated individuals, for whom decline occurred up to 16 years before dementia (Amieva et al., 2014). It also demonstrates the protective role of education in the clinical trajectory preceding Alzheimer's dementia. No schooling was independently associated with cognitive impairment in a cross-sectional Indian study (Konda et al., 2018).

Employment: Chanda and Mishra (2019), in their study, reported that elderly who have never worked before have the worst mean cognitive health after adjustment for demographic and economic factors. Another SAGE study showed that retirement from a highly complicated job affects cognition negatively in old age. If the discontinuation from an intellectually-challenging appointment is sudden, the decline in cognition is pronounced. Working in the informal sectors for an extended period stimulates cognition up to a certain time (Fernández-niño et al., 2018).

Ethnicity: A collaborative cohort by Lipnicki and others (2017) described race/ethnicity as risk factors for cognitive decline in their study. They reported a slightly faster decline in the MMSE with age in the Asian group compared to the white group.

Gender: Lipnicki et al (2017) also reported a faster decline in MMSE scores for females than males. Women have shown poorer memory performance than men in studies from developing countries or where women have historically not been given the same educational opportunities as men, including India (Lee et al., 2014) and China (Lei et al., 2012). There is lack of data from India to indicate a gender differential incidence or prevalence of dementia, although the prevalence of most vascular risk factors is significantly higher among men than among women (Ravindranath and Sundarakumar, 2021; Geldsetzer et al., 2018). Female gender was associated with cognitive impairment in a cross-sectional Indian study on 499 elderly living in South India (Samuel et al., 2016).

Marital Status: Widowhood can cause reductions in intellectual and cognitive stimulations, accelerating cognitive decline (MacKinnon-Lee and Bahr, 2020; Meng et al., 2018, Turner et al., 2015). Studies indicate that being married or living with someone (adult children, partner) show significantly lower cognitive decline than those who are single or living alone (MacKinnon-Lee and Bahr, 2020; Elovainio et al., 2018; Caroll, 2015; Mousavi-Nasab et al., 2012). Widowhood status is a significant risk factor for AD. Fan et al (2015) demonstrated an association between the risk of all-cause dementia and widow status. A meta-analysis by Sommerlad et al (2018) reported an association between widowhood and all-cause dementia, but a similar association was not found between widowhood and AD or vascular dementia. A study conducted in Ludhiana (n=3038, age=60 years and more) found widowed/unmarried status to be a strong predictor for cognitive impairment, particularly severe cognitive impairment (Sengupta et al., 2014). Another cross-sectional study in Himachal Pradesh also reported that old-old, illiterate and widowed exhibit a higher risk of cognitive impairment (Sharma et al., 2013).

Stress and Depression: Elevated cortisol levels indicative of physiological stress were observed in patients with AD compared to the control group (Wang et al., 2018; Ennis et al,. 2017; Lara et al., 2013; Zverova et al., 2013). Early adult depression is a risk factor for dementia at a more advanced age, including AD (Vilalta-Franch et al., 2013; Ricci et al., 2012). Zverova et al. (2013) observed a greater odds ratio for cognitive decline in the presence of higher cortisol levels in patients with AD and symptoms of depression. Wu et al (2018) observed hippocampal atrophy and Aβ peptide deposition in some patients with major depression in middle age Depression was one of the correlates of cognitive impairment in a cross-sectional study conducted among 100 randomly selected urban elderly persons in Hyderabad (Konda et al., 2018).

Attention Deficit Hyperactivity Disorder (ADHD): Zhang et al (2021) found that parents of individuals with ADHD had 34% higher risk of dementia than parents of individuals without ADHD. The risk of AD, the most common type of dementia, was 55% higher in parents of individuals with ADHD. There was a greater likelihood of individuals with ADHD to have parents with early-onset dementia than late-onset.

Viral Diseases: Liu and colleagues (2021) reported that viral infections could contribute to neurodegeneration based on laboratory experiments. They showed that certain viral molecules facilitate the intercellular spreading of protein aggregates that are hallmarks of brain diseases like Alzheimer's.

Inadequate Sleep: According to a study published by Proserpio et al (2018), sleep disorders have a two-way relationship with AD; sleep disorders arise during early dementia and worsen with the progress of dementia. Also, sleep disorders can lead to an increased risk of dementia. Individuals with sleep disorders have an increased risk of developing dementia (Silva et al., 2019; Silva et al., 2019; Shi et al., 2018).

Hearing Loss: Hearing loss is also associated with an elevated risk of cognitive decline or dementia (Lin et al., 2013). A meta-analysis of prospective cohort studies revealed that the relative risk of hearing impairment on incident AD and MCI was 2.82 (95% CI: 1.47–5.42) (Zheng et al., 2017). Another meta-analysis published by the Lancet Commission showed that hearing loss could increase the risk of incident dementia nearly two-fold (RR = 1.94, 95% CI: 1.38–2.73) (Livingston et al., 2017).

Other Risk Factors in Context to India: Social inequalities in early or midlife may be associated with poorer cognition (Wu et al., 2020; Cadar et al., 2018; Marden et al., 2017), as well as frailty (Hoogendijk et al., 2018), and multimorbidity (Dugravot et al., 2020; Barnett et al., 2012) in later life. A cross-sectional study from central India found that the onset of AD dementia was delayed by 5 years and frontotemporal dementia by 3 years in bilingual people compared with monolingual people (Alladi et al., 2017; 2013). The protective effect of multilingualism remained after controlling for education.

Another factor is the change in the social environment caused by the ongoing transition from the joint family system (three generations living together) to nuclear families, which results in less cognitive engagement for the elderly (Dhillon et al., 2016). Living alone was a risk factor for dementia in a study conducted in South India (Lalu et al., 2018) on 100 elderly aged 65 years or more. They also reported that reduced fruit consumption, comorbidities such as dyslipidemia and reduced hearing were associated with high dementia risk. Nutritional deficiencies contribute significantly in the pathogenesis of dementia (Ravindranath and Sundarakumar, 2021). The risk of dementia was associated with vitamin D deficiency (Goodwill et al., 2017). Increasing age is a non-modifiable risk factor of dementia in India (Lalu et al., 2018; Samuel et al., 2016). A recent study by Selvamani and Arokiasamy (2021) reported that there was a positive and significant association between adult socio-economic status and cognitive functioning. Among older adults in India and China, height was significantly and positively associated with improved cognitive functioning. In India, wealthier older adults had higher cognitive functioning in middle age; however, wealth differences narrowed with age (Selvamani and Arokiasamy, 2021).

5.3.6. Environmental Risk Factors

A systematic review has elucidated that environmental risk factors may explain a substantial proportion of unexplained risk factors for dementia: air pollution (higher levels of nitrogen oxides, environmental tobacco smoke, particulate matter, ozone concentration), toxic heavy metals (lead), other metals (aluminium, calcium, cobalt, copper, iron, manganese), other trace elements (silicon, selenium), pesticides, vitamin D deficiency, and low frequency electric and magnetic fields (Killin et al., 2016).

5.4. RISK REDUCTION OF COGNITIVE DECLINE AND DEMENTIA

WHO (2019) has given detailed guidelines for risk reduction of cognitive decline and dementia. These include the following aspects:

Physical Activity Interventions: A physically active lifestyle is linked to brain health. WHO (2019) recommends that adults aged 65 years and above should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week, or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity.

Tobacco Cessation and Alcohol Use: Any type of intervention aimed at tobacco and alcohol cessation shall be beneficial (WHO, 2019).

Nutritional Interventions: Promising dietary approaches associated with better cognitive function include the Mediterranean diet (Singh et al., 2014; Wu & Sun, 2017), Dietary Approaches to Stop Hypertension (DASH) (Berendsen et al., 2017; Morris et al., 2015a; 2015b; Wengreen et al., 2013); and the brain health-specific Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet. WHO's recommendations for diet are based on the Mediterranean-like diet.

Cognitive Interventions and Social Activity: The proof of cognitive stimulation in reducing the risk of dementia was insufficient, and no recommendation was made by WHO (2019), which stated that

ognitive training should be offered to older adults with normal cognition and MCI to reduce the risk of cognitive decline and/or dementia. Social participation and social support are strongly linked to good health and wellbeing throughout life, and social inclusion should be supported over the life course.

Weight Management: A link has also been established between excess fat mass and cognitive impairment (Xu et al., 2011). WHO (2019) has outlined recommendations for weight management, which include both dietary advice and physical activity.

Management of Hypertension, Diabetes and Dyslipidemia: WHO (2019) has stressed on the appropriate management of these disorders.

Management of Depression: There is a substantial evidence linking depression to cognitive decline and dementia. There is currently insufficient evidence to recommend antidepressant medicines for reducing the risk of cognitive decline and/or dementia. WHO's recommendation for depression include psychosocial / non - pharmacological treatment and advice.

Management of Hearing Loss: There is insufficient evidence to recommend hearing aids to reduce the risk of cognitive decline and / or dementia. However, hearing loss interventions can substantially improve outcomes for older people in multiple domains (WHO, 2019).

Dietary Recommendations

A Mediterranean - like diet may be recommended to adults with normal cognition and MCI. A healthy diet contains:

- Fruits, vegetables, legumes (e.g. lentils, beans), nuts and whole grains (e.g. unprocessed maize, millet, oats, wheat, brown rice).
- At least 400 g (five portions) of fruits and vegetables a day. Potatoes, sweet potatoes, cassava and other starchy roots are not classified as fruits or vegetables.
- Less than 10% of total energy intake from free sugars, which is equivalent to 50 g (or around 12 level teaspoons) for a person of healthy body weight consuming approximately 2000 calories per day, but ideally less than 5% of total energy intake for additional health benefits. Most free sugars are added to foods or drinks by the manufacturer, cook or consumer, and can also be found in sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates.
- Less than 30% of total energy intake from fats. Unsaturated fats (found in fish, avocado, nuts, sunflower, canola and olive oils) are preferable to saturated fats (found in fatty meat, butter, palm and coconut oil, cream, cheese, ghee and lard) and trans-fats of all kinds, including both industrially produced trans-fats (found in processed food, fast food, snack food, fried food, frozen pizza, pies, cookies, biscuits, wafers, margarines and spreads) and ruminant trans-fats (found in meat and dairy foods from ruminant animals, such as cows, sheep, goats, camels and others). It is suggested to reduce the intake of saturated fats to less than 10% of total energy intake and trans-fats to less than 1% of total energy intake. In particular, industrially-produced trans-fats are not healthy and should be avoided
- Less than 5 g of salt (approximately 1 teaspoon) per day and use iodized salt.

WHO, 2019

6. CONCLUSIONS & RECOMMENDATIONS

Genetic variations interact with early life environment and affect child's brain development mainly through epigenetic mechanisms; leading to individual differences in human cognitive abilities.

There are multiple factors that affect brain health from conception till old age: modifiable and non-modifiable. The modifiable factors include diet, physical activity, social engagement, cognitive activity, smoking and alcohol consumption.

Strategies to promote brain health throughout the lifespan should target individuals at each phase of life to adopt a healthy lifestyle (diet and physical activity), be engaged in cognitively stimulating activities and be socially active.

In the Indian context, there are few studies conducted in the last decade to understand the role of nutrition and lifestyle factors on brain health.

6.1. CONCLUSIONS

Good brain health state enables an individual to comprehend their own abilities and adjust their cognitive, psychological, emotional and behavioural functioning according to various life events in order to cope with these situations optimally. Disruptions in normal brain growth and/or functioning occur throughout life and present as neurodevelopmental conditions such as epilepsy, brain tumours, intellectual developmental disorders, cerebrovascular disease, headache, autism spectrum disorders, neuro-infections, multiple sclerosis, traumatic injury, Parkinson's disease and neurological disorders resulting from malnutrition (WHO, 2021).

The first 1000 days lay the foundation for brain growth and development of the child. A malnourished mother does not get the calories and nutrients that are needed to support the baby's development, the baby is at high risk for developmental delays, birth defects and cognitive deficits. Food provides the fuel for much of the extraordinary brain development that takes place in early childhood, and nutrition during this period remains critically important. Thus, a malnourished child grows into a malnourished adolescent with problems in learning, emotional and behavioural circuits. Such adults face difficulties to pursue higher education or get good work opportunities further causing them to lead a financially poor life. Children born in such low-income families have poorer learning abilities and the vicious cycle continues. Malnutrition at any stage, whether pregnancy, infancy or childhood is detrimental for brain growth and maturation. Deprivation during a critical period of brain development can have long lasting, often irreversible effect on brain development. Science suggests that it is a far better policy to promote brain development through nutritional deficit prevention programs than to depend on replacement therapy once a deficit has occurred.

Failure to provide adequate macronutrients or key micronutrients at critical periods in brain development has a lifelong effect on a child. In addition to generalized macronutrient under nutrition, deficiencies of individual nutrients may

have a substantial effect on neurodevelopment. All **nutrients** are important for brain development; however, some seem to have a significant effect on developing brain circuits during the third trimester and early neonatal period. These include protein, iron, zinc, selenium, iodine, folate, vitamin A and D, choline, and long-chain polyunsaturated fatty acids.

In recent years, considerable information has been accumulated on the relationship between **gut microbiome** and brain function through the gut brain axis. The gut microbiome is highly sensitive to negative external lifestyle aspects, such as diet, sleep deprivation, circadian rhythm disturbance, chronic noise, and sedentary behaviour, which are also considered as important risk factors for the development of Alzheimer Disease. Data on the beneficial effects of dietary fibres and probiotics through management of gut microbes is strongly emerging.

Evidence exists to support a positive relationship between **physical activity**, fitness, cognitive function, and academic achievement. Physical fitness is associated with differences in the volume of specific regions of the brain related with learning and cognitive function. Physical activity, healthy diet and the interaction between physical activity and nutrition are significant predictors of reading, math and science scores. Studies have shown that the practice of physical activities is capable of promoting an increase in hippocampal volume, in addition to increasing plasma BDNF concentrations in healthy elderly, indicating a possible neuroprotective effect.

Aerobic exercise is beneficial to cognitive functioning; resistance training may play an important role in improving cognitive function; prescription of both aerobic and resistance training (ie, multi-component training), in accordance with exercise recommendations, for the older age group to specifically improve cognitive functions; tai chi (non-traditional modes of exercise that may be suitable for less functional populations) improved cognitive function in older adults. An exercise prescription of between 45 and 60 min in duration, of moderate or vigorous intensity and of any frequency or length is beneficial to cognitive function (Northey et al., 2018).

Encouraging older adults to participate in senior citizen clubs or to have frequent contacts with adult children by phone or letters may help reduce cognitive decline in later life among older adults. Participation in a variety of **formal social activities** may also have a beneficial effect on preventing cognitive decline in older adults. Traveling, having discussions, playing games and participation in cultural events and social sports helps stimulating the brain (Sommerlad et al., 2019).

Several elements are associated with a greater cognitive reserve, such as educational level, occupational activities, leisure activities, physical activities and the integrity of relationships network. **The educational experiences** provide the foundation for continued intellectual stimulation across the life course, resulting in improved cognitive functioning in late adulthood. Education may cultivate the knowledge, skills, and ability necessary for continued participation in intellectually demanding activities (e.g., reading, taking courses) well into later adulthood.

Although there is a large body of evidence suggesting that **cognitive training** can improve reasoning, memory, and speed of processing, the validity of these connections has yet to be documented in large randomized control trials. It is important to note that no specific “brain game” or “brain exercise” has shown to be effective on brain health (Mintzer et al., 2019).

Smoking increases oxidative stress by increasing the production of free radicals leading to oxidative damage in the brain. Similarly, alcohol consumption leads to loss of brain cells and combination of both can have a detrimental effect on cognitive impairment and lead to Alzheimer's disease incidence.

Sleep is important for brain plasticity and memory consolidation (Abel et al., 2013) and sleep disturbance is a common problem for older people as well as patients with mild cognitive impairment and dementia (da Silva, 2015; Benito-León et al., 2014). Several cross-sectional or prospective studies reported that shorter and longer sleep duration may be important risk factors for subsequent cognitive impairment (Spira et al., 2017; da Silva, 2015; Benito-León et al., 2014). Longer sleep duration may increase the risk of dementia, function as an early symptom of dementia, or be associated with sleep disorder-related breathing and smoking habits (Benito-León et al., 2014).

6.2. STRATEGIES TO PROMOTE BRAIN HEALTH THROUGHOUT THE LIFESPAN

Barnett and others (2013) suggest that some risk for cognitive decline and dementia could be reduced through the protection of cognitive health throughout the lifespan (Figure 10). Here we discuss the strategies to promote brain health at every stage of life.

6.2.1. Pregnancy

Pre-natal: The mother's age, socio-economic status, maternal health, substance use, and nutrition influence the brain development in the foetus. Imparting nutrition education in adolescent girls regarding healthy weight and multi-nutrient supplementation in order to correct micronutrient deficiencies will be crucial to eradicate anaemia and other deficiency disorders. Focus should be on nutritional counselling, screening for nutrient deficiencies and maintaining a healthy body weight.

Peri-natal: Maternal malnutrition can result in both global and specific neurodevelopmental sequelae. Therefore, the diet of the pregnant mothers should be nutritious and be rich in both macro- and micro- nutrients. Macronutrients that affect early brain development are protein and long chain poly unsaturated fatty acids. Micronutrients essential during this phase are vitamin B (folate, B6, B12), vitamin D, antioxidant vitamins (E & C), choline, minerals such as iron, iodine and zinc. Maternal supplementation with multiple micronutrients (MMN) showed long-term benefits for child cognitive development (cognitive, motor, and socio-emotional). During gestation, non-nutritional factors, including maternal high blood pressure, diabetes mellitus, and stress, can affect nutritional status of the foetal brain. These need to be carefully monitored throughout pregnancy.

Post-natal: Postpartum recovery is essential for both the mother and her child. Balanced diet and exercise are important to restore muscle tone and connective tissue. Diet should contain calcium, choline, folate, iron, omega-3s and vitamin D. Managing stress and sleep is crucial to mother's overall health and well-being so that she can take care of her new-born. Continued breastfeeding and nutrition support from spouse and family plays an important part to reduce the risk of depression. Thus, nutritional support of the newborn includes nutritional counseling of the mother. Maternal mental health needs to be addressed so that she can provide support to her young one.

Public health policies should emphasize access to quality food for pre-conceptional, pregnant, and lactating women. Guidelines should support breastfeeding for infants during the first year and more oversight of the quality of food that children are offered from 1 to 3 years, when they are most vulnerable to the vagaries of parental diets.

6.2.2. Infancy and Childhood

- Parenting programmes are interventions to improve parenting interactions, knowledge, behaviour, attitudes, beliefs, and practices (Britto et al., 2016). Evidence supports the positive effects of such programmes on direct measures of children's cognitive and language development.
- Aspects of nurturing care such as Kangaroo Mother Care, which promotes thermal sufficiency in preterm infants and promotes early bonding are important.
- Breastfeeding may improve cognitive development through several mechanisms, related both to the composition of breast milk and to the experience of breastfeeding. So, exclusive breastfeeding should be promoted in the first six months of life. Breastfeeding has clear short-term benefits for child health, reducing mortality and morbidity from infectious diseases, encouraging healthy food preferences, and promoting the establishment of a healthy gut microbiome (Goldsmith et al., 2015).
- Severe PEM in early stages of life can affect learning and lead to poor cognitive development that is often irreversible. Toddlers and school-going children should be fed a healthy, wholesome and nutritious diet which is rich in both macro- and micro-nutrients. To prevent PEM, the diet should contain high quality whole grain cereals and grains, pulses and legumes. Protein should be of high biological value and supplementary feeding should also be encouraged. Iron and iodine are crucial micronutrients that affect brain development and function in young children. Given the wide prevalence of multiple micronutrient deficiencies in malnourished children, there is a need to implement interventions that combine micronutrient interventions with appropriate infant and young child feeding (Britto et al., 2016).
- Inadequate nutrition in children hinders their developmental potential in motor, cognitive and socio-emotional abilities. Therefore, preventing or reversing developmental losses is crucial to foster economic development and reduce economic disparities. Following strategies would be effective:
  - Iron food fortification
  - Salt iodization
  - Nutrition education to mothers
  - Food supplementation (iron, folic acid, essential fatty acids) in food-insecure populations
- Poor parental food habits and food insecurity affect the diets of children and need to be addressed to ensure optimal nutrition and brain development from pregnancy though early childhood. Importance of breakfast and mid-day meals should be emphasized so that parents make extra efforts into the food that their children consume.
- Exposure of the infant to traumatic events such as maltreatment by parents, bullying, terrorism, exposure to war, and violence can adversely impact brain development of the child. Psychological neglect early in life also impacts brain development. Interventions to improve the home environment and the quality of caregiver-infant interaction are also recommended to complement and enhance the effect of improved nutrition.
- Apart from diet, regular physical activity and sleep health (duration, timing and quality) also need to be considered for adequate brain health of children.
- Pre-schooling is important. Formal and non-formal or community-based preschools in LMICs improved scores on direct measures of children's cognitive development and psychosocial development (Britto et al., 2016).

- Cognitive enrichment early in life may account for some of the variation in cognitive ability in adulthood. Children growing up in higher-SES homes tend to be exposed to more complex and cognitively stimulating environment. Cognitive enrichment is associated with improved cognition in youth independent of stress exposures. Therefore, children should be given cognitively stimulating environment whereby they are encouraged to study and participate in intellectually demanding activities to improve cognitive function.
- Among children, disorders such as attention deficit hyperactivity disorder (ADHD) and dyslexia impair specific cognitive functions that can considerably impact a child's educational attainment.
- Exposure to healthy play time, interactive digital media (for education and recreation) as well as music enhances cognition in children.

6.2.3. Adult and Mid-Life

- ***Diet***: Higher diet quality in terms of a higher intake of healthy food choices is a significant potential method for lowering the global burden of cognitive decline. Evidence exists to support the 'whole diet approach' theory that a balanced diet as a whole, rather than single nutrients is beneficial for brain health. A balanced diet should be encouraged via nutrition counselling in early adult life along with regular physical activity to promote a healthy lifestyle. Mediterranean diet, Nordic diet, DASH and MIND diets have been linked with low risk of cognitive decline and dementia.
- ***Healthy Gut***: Gut microbiomeinteract with brain in multiple ways and is involved in cognition. Consuming foods rich in pre- and pro- biotics should be encouraged to maintain a healthy cognitive reserve.
- ***Physical Activity***: Physical activity is important. WHO has recommended adults to undertake 150 minutes of moderate-to-vigorous physical activity for their physical and mental well-being.
- ***Cognitive Activity***: Brain-stimulating activities such as strategy-based games, stimulation games, cross-word puzzles should be undertaken regularly.
- ***Reducing Dementia Risk***: Dementia risk is strongest for exposure in midlife and that usually reflects lifelong patterns of behaviour and so individuals who maintain a healthy lifestyle by eating well and exercising regularly are likely to benefit from cognitive decline over decades.
- ***Diseases***: Poor lifestyle during adulthood often paves the way for lifestyle-related diseases during mid-life and old age. Care should be taken to ensure prevention and delay of hypertension, diabetes mellitus, dyslipidemia, cardiovascular diseases, atherosclerosis, heart diseases etc. Anxiety and depression need to be diagnosed and managed as they increase the odds for cognitive decline.
- ***Sleep***: Sleep disorders need to be corrected as they increase dementia risk.
- ***Stress***: Stress management is crucial in mid-life as it increases the risk for Alzheimer's disease due to increased cortisol levels.
- ***Pollution***: Pollution need to be reduced. Governments need to address this issue at the global level to provide a clean and pollution-free environment for optimum brain health.

6.2.4. Old Age

- ***Diet***: Mediterranean diet with olive oil or nuts have been shown to improve cognition in the elderly while a diet of high sugars,

carbohydrates and glycaemic loads lead to insulin resistance, impaired glucose metabolism and type 2 diabetes mellitus which are all known risk factors for Alzheimer's disease. Nutrition counselling and omega fatty acid supplementation can prove beneficial to brain health.

- ***Physical Activity***: Individuals with life-long exercise routine reveal larger brain volume and improved executive function than inactive older adults. Since there are no separate recommendation by the WHO for the elderly, they should also aim to achieve 150 minutes of moderate to vigorous PA.
- ***Smoking and Alcohol***: The elderly should avoid smoking and alcohol consumption as it predisposes to Alzheimer's disease in addition to cognitive decline.
- ***Diseases***: Comorbidities are common and needs to be addressed. Monitoring and management of blood pressure, blood sugar, lipids and vascular risk should be done on a regular basis. Screening at geriatric clinics for frailty, sarcopenia, cachexia is important.
- ***Cognitive Training***: Mental engagement /cognitive training interventions (specific training in either memory, reasoning or speed of processing) have shown beneficial in improving cognition. Older adults who have retired need to keep themselves occupied with brain stimulating activities or undertake involuntary charitable work to keep themselves mentally active.
- ***Social Engagement***: Talking with their adult children on the phone is likely to provide older adults emotional support and intimacy. Participation in a number of different organizations reduce the onset of long-term cognitive decline. Care and participation in a variety of social groups is effective for prevention of cognitive decline. The senior centres could provide diverse group activities for the elderly including painting, calligraphy, origami, gardening, playing musical instruments, acting and exercise programs.

6.3. RECOMMENDATIONS FOR FUTURE RESEARCH

The role of nutrition and lifestyle factors in brain development, function and decline is on area which is garnering increasing attention in the recent years. Some pioneering research was carried out in establishing brain growth patterns and influence of genetic and environmental factors on these, several decades ago. However, with the epidemiological and societal transition there is a dire need to examine such influences in light of these changes.

Moreover, the factors that have been derived are based on studies which are observational in nature and unidentified confounders may bias the results. These studies often lack consistency and detail in description or categorization of lifestyle activities and sometimes in the cognitive outcomes measured as well. Longer duration longitudinal studies or cohorts are needed to get a better insight into each of the lifestyle factors that affect cognition.

In the Indian context, there are few studies conducted in the last decade to understand the role of nutrition and lifestyle factors on brain health. While a significant number of researches are now focussing on old age, the period of adulthood is being overlooked. In fact, young adulthood and middle age are the crucial periods for determining the cognitive health in old age. Moreover, many of these studies are cross-sectional in nature and hence getting a life course perspective is difficult. It is therefore very vital to conduct large longitudinal studies as well as study established cohorts to examine the influence of environmental exposures on not only early life brain development but also the influence on the brain health trajectory through the life cycle, including adulthood.

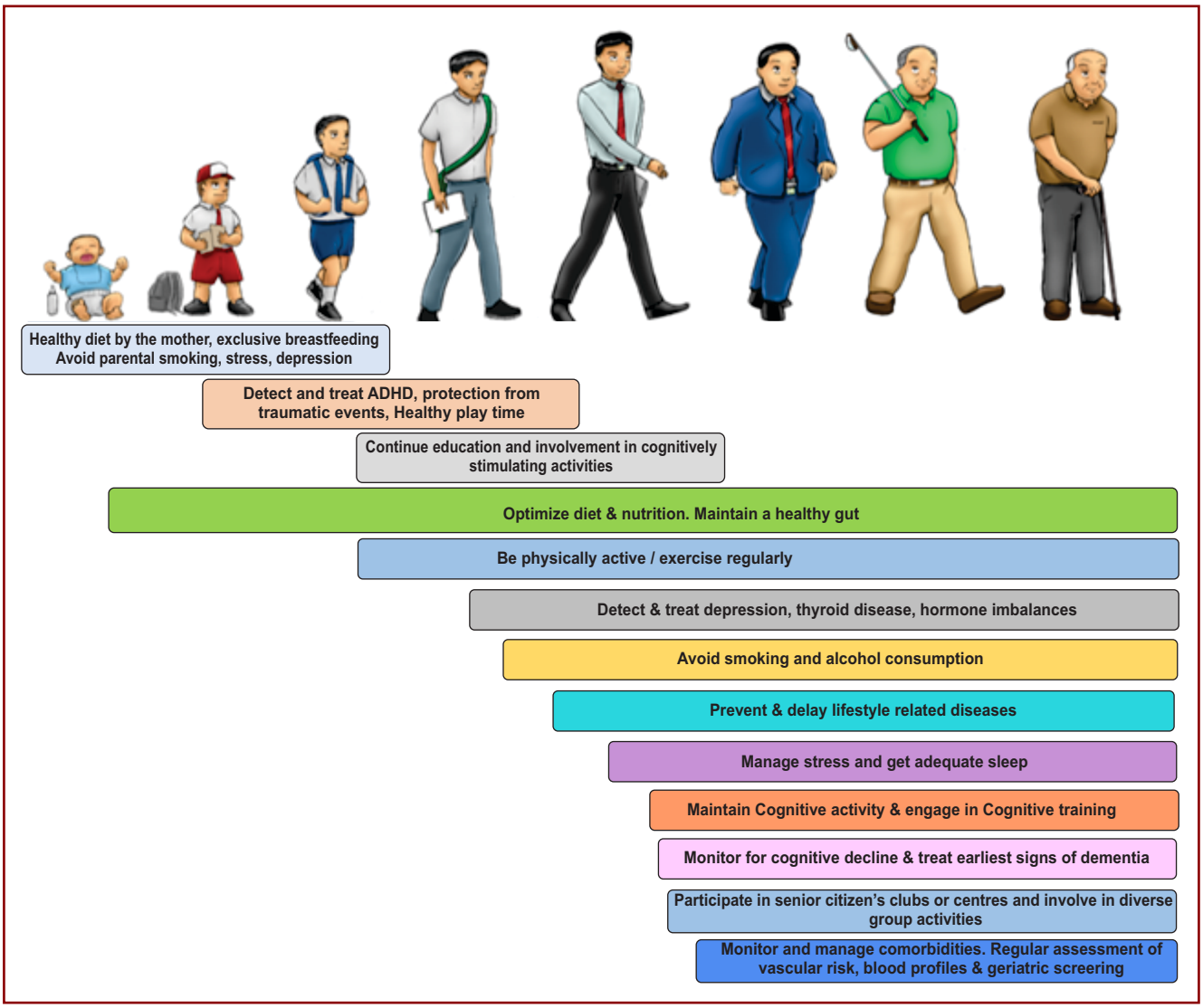

Figure 6: Preventing Cognitive Decline and Promoting Brain Health throughout Lifespan

Source: Adapted from Barnett et al., 2013

Unlike noncommunicable diseases like cardiovascular disorders, diabetes and cancer, there is a dearth of epidemiological data on cognitive impairment and dementias. In fact, large national surveys should include these disorders to estimate their prevalence and related epidemiological data. The Longitudinal Ageing Study in India (LASI, 2020) conducted by International Institute of Population Studies and facilitated by Ministry of Health and Family Welfare did capture the reported prevalence of Alzheimers disease among 44 to 99 year olds as only 0.4 % (IIPS, 2020). However, these were previously diagnosed cases and hence there is a need to include screening and assessment for cognitive dysfunction so as to detect undiagnosed cases in such surveys.

Keeping the lifecourse approach in view, some areas of research in India which need to be strengthened include studies on:

- The complex interactions between genes, in utero environment and the developing brain, including prenatal environmental factors and their effect on gene expression.
- The influence of lifestyle exposures during pregnancy like malnutrition, stress, infections, inflammation, diabetes on brain development.
- The effect of early life exposures like caregiver interaction, deprivation on cognitive development and function in young children, both longitudinal and cross-sectional studies at different ages.
- Comparison of breast fed, partially breast fed and non breast fed infants in terms of their cognitive development at multiple time points in the first two years.
- More in-depth information on the role of the gut brain axis and its role in brain development, function and decline.
- The effect of lifestyle factors such as stress, screen time, sleep, academic pressure etc., on cognitive development and performance during childhood.
- The effect of the Covid pandemic with prolonged school closures, low peer interaction, social isolation, on cognitive health of children.
- Assessment of the health and lifestyle of middle aged adults and also the influence of these on cognition.
- Role of nutritional and dietary components on promoting brain heatlh and preventing cognitive decline.
- Investigation of the role of vegetarian diets on cognitive health
- A study of ayurvedic literature and substantiating the claims of neuroprotective herbs / plants, therein by robust clinical trials.

Since most of the available literature is based on research carried out in countries other than India, it becomes very important to conduct such investigations in the Indian context so as to validate the findings further as well as examine its applicability based on the Indian genotype.

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ANNEXURE I

Keywords Used as Search Terms in PUBMED and Sample Search Strategy Adopted for the Review

A. Keywords

The following keywords were included in the search: brain development/ cognitive development/ cognition, cognitive decline, cognitive impairment/ mild cognitive impairment (MCI), cogntitive reserve, cognitive training, cognitive improvement, physiology, critical periods, first 1000 days, heredity, genes, genetics, genetic influence, genetic factors, environment, lifestyle choices, physical activity, physical fitness, aerobic exercise, yoga, meditation, age, gender, marital status, nutrition, malnutrition (maternal and child), stunting, wasting, nutrients, macronutrients, micronutrients, iron/iron deficiency, folic acid/folate/ deficiency, docosahexaenoic acid/DHA, eicosapentaenoic acid/EPA, vitamin D/deficiency, Iodine/deficiency, protein/deficiency, nutrition, vitamins, vitamin deficiency, microbiome, microbiota, probiotics, synbiotics, poor diet, dietary patterns, food groups, food intake, dietary intake, diet, breakfast, mid-day meals, Ayurveda, herbs, Alzheimer's disease, dementia, risk factors, social activities, social participation, depression, pollution, frequency of contact, early childhood experiences, early life adversities, education, schooling, employment, substance use/abuse, smoking, alcohol, sleep, nurturing care, caregiving, breastfeeding, media, television, social media, screen time, play, gaming, video games, vedic education (child and parental), home environments, socio-economic status, poverty, family income, social background, maternal mental health, maternal depression, anxiety, intra-uterine growth retardation, postnatal growth failure, low birth weight, child abuse, violence, neglect, brain exercises, India, Indian children, Indian context and included MeSH terms (Medical Sub Headings).

B. Sample search strategy adopted

- ((Iron[MeSH Terms]) OR (Folic Acid[MeSH Terms])) AND (Brain development[MeSH Terms])
- ((Iron[MeSH Terms]) OR (Folic Acid[MeSH Terms])) AND (Brain development[MeSH Terms]) AND India
- (Iron[MeSH Terms]) AND (Brain Development[MeSH Terms])
- (Iron[MeSH Terms]) AND (Brain Development[MeSH Terms]) AND India
- (Folic Acid[MeSH Terms]) AND (Brain Development[MeSH Terms]) AND India
- (Iodine[MeSH Terms]) AND (Brain Development[MeSH Terms]) AND India
- ((DHA[MeSH Terms]) OR (EPA[MeSH Terms])) AND (Brain development[MeSH Terms]) AND India
- (Iron deficiency[MeSH Terms]) AND (Cognitive function[MeSH Terms]) AND India
- (Folic Acid[MeSH Terms]) AND (Cognitive function[MeSH Terms]) AND India
- (Folic acid deficiency[MeSH Terms]) AND (Cognitive function[MeSH Terms]) AND India
- (Iodine[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (Iodine[MeSH Terms]) AND (Cognitive function[MeSH Terms]) AND India
- (Iodine deficiency[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (Protein[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (protein deficiency[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (Diet[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (poor diet[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (poor dietary intake[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (Vitamins[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (vitamin deficiency[MeSH Terms]) AND (Cognitive function[MeSH Terms])

ANNEXURE I

Keywords Used as Search Terms in PUBMED and Sample Search Strategy Adopted for the Review

A. Keywords

The following keywords were included in the search: brain development/ cognitive development/ cognition, cognitive decline, cognitive impairment/ mild cognitive impairment (MCI), cogntitive reserve, cognitive training, cognitive improvement, physiology, critical periods, first 1000 days, heredity, genes, genetics, genetic influence, genetic factors, environment, lifestyle choices, physical activity, physical fitness, aerobic exercise, yoga, meditation, age, gender, marital status, nutrition, malnutrition (maternal and child), stunting, wasting, nutrients, macronutrients, micronutrients, iron/iron deficiency, folic acid/folate/ deficiency, docosahexaenoic acid/DHA, eicosapentaenoic acid/EPA, vitamin D/deficiency, Iodine/deficiency, protein/deficiency, nutrition, vitamins, vitamin deficiency, microbiome, microbiota, probiotics, synbiotics, poor diet, dietary patterns, food groups, food intake, dietary intake, diet, breakfast, mid-day meals, Ayurveda, herbs, Alzheimer's disease, dementia, risk factors, social activities, social participation, depression, pollution, frequency of contact, early childhood experiences, early life adversities, education, schooling, employment, substance use/abuse, smoking, alcohol, sleep, nurturing care, caregiving, breastfeeding, media, television, social media, screen time, play, gaming, video games, vedic education (child and parental), home environments, socio-economic status, poverty, family income, social background, maternal mental health, maternal depression, anxiety, intra-uterine growth retardation, postnatal growth failure, low birth weight, child abuse, violence, neglect, brain exercises, India, Indian children, Indian context and included MeSH terms (Medical Sub Headings).

B. Sample search strategy adopted

- ((Iron[MeSH Terms]) OR (Folic Acid[MeSH Terms])) AND (Brain development[MeSH Terms])
- ((Iron[MeSH Terms]) OR (Folic Acid[MeSH Terms])) AND (Brain development[MeSH Terms]) AND India
- (Iron[MeSH Terms]) AND (Brain Development[MeSH Terms])
- (Iron[MeSH Terms]) AND (Brain Development[MeSH Terms]) AND India
- (Folic Acid[MeSH Terms]) AND (Brain Development[MeSH Terms]) AND India
- (Iodine[MeSH Terms]) AND (Brain Development[MeSH Terms]) AND India
- ((DHA[MeSH Terms]) OR (EPA[MeSH Terms])) AND (Brain development[MeSH Terms]) AND India
- (Iron deficiency[MeSH Terms]) AND (Cognitive function[MeSH Terms]) AND India
- (Folic Acid[MeSH Terms]) AND (Cognitive function[MeSH Terms]) AND India
- (Folic acid deficiency[MeSH Terms]) AND (Cognitive function[MeSH Terms]) AND India
- (Iodine[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (Iodine[MeSH Terms]) AND (Cognitive function[MeSH Terms]) AND India
- (Iodine deficiency[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (Protein[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (Protein deficiency[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (Diet[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (Poor diet[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (Poor dietary intake[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (Vitamins[MeSH Terms]) AND (Cognitive function[MeSH Terms])
- (Vitamin deficiency[MeSH Terms]) AND (Cognitive function[MeSH Terms])

Table 2: Characteristics of Human Studies on the Intake of Macronutrients in Relation to Cognition

Macro-nutrients	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Protein	Cross-Sectional	US	Li et al., 2020	The National Health and Nutrition Examination Survey (NHANES) 2011–2014 Non-Institutionalized US Adults Aged 60 Years and Older.	Protein intake from total animal foods, total meat, eggs and legumes were associated with a better performance on certain cognitive tests. An adverse association between higher protein intake from milk and milk products and cognitive function was observed.
	Systematic Review and Meta-Analysis	NA	Coelho-Júnior et al., 2021	Nine Cross-Sectional Studies on 4929 Older Adults were Included in the Qualitative Analysis. Overall Cognitive Function was Examined in 6 Studies.	Results from the meta-analysis suggested that Memory and protein intake were positively correlated in 3 studies. Visuospatial, verbal fluency, processing speed, and sustained attention were each positively associated with protein consumption in only one study. There were no significant association between protein consumption and global cognitive function in older adults, regardless of gender.
SFA	Longitudinal	US	Okereke et al., 2012	n=6183 Elderly Females.	Higher SFA intake was associated with worse global cognitive and verbal memory trajectories, whereas higher MUFA intake was related to better trajectories.
LCPUFA	Systematic Review	NA	Delgado-Noguera et al., 2015	n=1567 Pregnant and Breastfeeding Mothers in High-Income Countries.	LCPUFA supplementation did not improve children's neurodevelopment, visual acuity or growth. In child attention at 5 years, weak evidence was found (one study) favouring the supplementation. Data on LCPUFA supplementation to breastfeeding mothers to improve neurodevelopment or visual acuity is inconclusive.

Macro-nutrients	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
	Systematic Review and Meta-Analysis	NA	Gould et al., 2013	n = 5272 Pregnant and Breastfeeding Mothers.	Omega-3 LCPUFA supplementation in pregnancy improves cognitive or visual development is inconclusive.
	Randomized Double-Blind Intervention	Mexico	Portillo-Reyes et al., 2014	n= 59 Children Aged 8–12 Years who were Moderately Malnourished (EPA-270 mg + DHA-180 mg) or Placebo (Soyabean Oil).	Better IQ, visuo-perceptive capacity, executive functioning and processing speed in three months was observed.
	RCT	Germany	Witte et al., 2014	n=65 Healthy Elderly (50-75 Years, 30 Females) Large Doses of ω-3 PUFA with 1.3g of EPA and 0.9g of DHA per day.	Improvement in executive function and cognition was observed.

Table 3: Characteristics of Human Studies on the Intake of Vitamins in Relation to Cognition

Micro-nutrients	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Vitamins (B_6, B_{12}, Folate and Riboflavin)	Longitudinal (4-Year Follow-Up Study)	UK	Hughes et al., 2017	n=155 Elderly Aged 60–88 Years.	Lower Vitamin B_6 status, as measured using Pyridoxal-5-Phosphate (PLP; <43 nmol/L) was associated with a 3.5 times higher risk of accelerated cognitive decline, after adjustment for age and baseline MMSE score. Lower dietary intake (0.9–1.4 mg/day) of Vitamin B_6 was also associated with a greater rate of cognitive decline. No significant relationships of dietary intake with cognitive decline were observed for the other B-Vitamins (Total Folate, B_{12} and Riboflavin).
Vitamin B_{12}	Systematic Review	NA	Doets et al., 2013	n=5254 Elderly.	No association or inconsistent associations between Vitamin B_{12} intake and cognitive function.
Vitamin B_{12}	RCT	UK	Dangour et al., 2015	n=201 Elderly Aged ⩾75 Years with Moderate Vitamin B_{12} Deficiency.	The correction of moderate Vitamin B_{12} deficiency did not have a beneficial effect on cognitive function in later life.
Vitamins (Niacin, Folate, B_6, B_{12})	Community-Based Multicentre Cohort	US	Qin et al., 2017	n=3136 Black and White Men and Women Aged 18–30 Years.	Higher intake of B vitamins throughout young adulthood was associated with better cognitive function in midlife.
B Vitamins	Prospective, Longitudinal Cohort Study	US	Agnew-Blais et al., 2015	n=7030 Postmenopausal Women Free of MCI.	Folate intake below the Recommended Daily Allowance may increase risk for MCI/probable dementia in later life. There were no significant associations between Vitamins B_6 or B_{12} and MCI/probable dementia.

Micro-nutrients	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
B Vitamins (Folate, B_2, B_6, B_{12})	Cross-Sectional	South Korea	Kim et al., 2014	n=321 Elderly Aged ⩾ 60 Years.	These results suggested that total B Vitamins intake is associated with cognitive function in cognitively impaired AD and MCI elderly, and the association is stronger in AD patients.
Antioxidant Vitamins (E, C)	Double-Blind, Placebo-Controlled Clinical Trial.	US	Galasko et al., 2012	n=78 Adults between 50-85 Years of Age with AD. 16 weeks with 800 IU/d of Vitamin E (α-tocopherol) plus 500 mg/d of Vitamin C plus 900 mg/d of α-Lipoic acid (E/C/ALA); 400 mg of Coenzyme Q 3 times/d; or Placebo.	The treatment raised the caution of faster cognitive decline.
	Prospective Cohort	Canada	Basambombo et al.,2016	n=5269 Elderly ⩾ 65 Years of Age.	Use of Vitamin E and C supplements is associated with a reduced risk of cognitive decline.
	Prospective	Netherlands	Nooyens et al., 2015	n=2613 Adults between 43-70 Years of Age.	Higher Lignan intake was linearly associated with less decline in global cognitive function, memory and processing speed. In the lowest quintile of Vitamin E intake, decline in memory was twice as fast as in all higher quintiles. Intakes of other antioxidants were not associated with cognitive decline.
	Cross-Sectional	US	Beydoun et al., 2015	n=1274 Adults (541 Men and 733 Women) between 30-60 Years.	1 standard deviation (~ 2.02 mg/1000 kcal) higher Vitamin E was associated with a higher score on verbal memory, immediate recall, and better language/verbal fluency performance, particularly among the younger age group. Women with higher Vitamin E intake had better performance on a psychomotor speed test.

Micro-nutrients	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Vitamins D	Longitudinal	US	Slinin et al., 2012	n=6257 Elderly Women Aged 65 Years and Older.	Lower 25(OH)D blood concentrations at baseline were associated with increased incidence of global cognitive decline.
	Post hoc Analysis of a Randomized Double-Blind Placebo-Controlled Trial	US	Rossom et al., 2012	n= 4034 Elderly Women ⩾65 Years.	No effect of a 7.8 year supplementation with 100 mg calcium carbonate and 400IU of Vitamin D3 on the incidence of Dementia, MCI, or other Cognitive measures.
	Meta-Analysis	NA	Annweiler et al., 2013	n= 44-5692 Community-Dwellers Adults.	Cognition improved in patients receiving Vitamin D supplementation ("before and after" approach). The between-group comparison of the cognitive scores at the end of the follow-up ("Comparative" Approach) did not show better cognitive scores in the supplementation arm compared to the comparative arm.

Table 4: Characteristics of Human Studies on the Effect of Iron Intakes on Cognition

Micro-nutrients	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Iron	RCT	Sweden	Berglund et al., 2013	n= 285 Marginally LBW (2000–2500 g) Infants received 0, 1, or 2 mg/kg/day of Iron Supplements from 6 Weeks to 6 Months of Age vs. 95 Normal Birth Weight Controls.	There were no significant differences in IQ/ cognitive functions at 3.5 years of age.
	Longitudinal	Australia	Cherbuin et al., 2014	n=1406 Cognitively Healthy Adults (52% Women). Mean Age 62.5 Years (Followed Up Over 8 Years).	Higher Magnesium intake was associated with a reduced risk of developing MCI. Higher intake of Potassium and Iron was associated with an increased risk of developing MCI.
	Longitudinal	China	Geng et al., 2015	n= 127 Infants (ID=35, IS=92).	Infants born IS and not ID, displayed a typical recognition memory response at two months of age.
	Longitudinal	US	Fuglestad et al., 2016	n=63 National and International Adoptees in the USA.	Lower scores on cognitive performance were seen within the IDA group compared to IS group.
	Cross-Sectional	Bangladesh	Tofail et al., 2013	n=434 Children, Aged 6-24 Months.	No difference between cognitive outcomes among IDA, ID or IS participants.
	RCT	China	Angulo-Barroso et al., 2016	n=1196 Infants.	Iron supplementation in infancy, with or without iron supplementation in pregnancy, improved gross motor test scores at 9 months.
	Cross-Sectional	Mexico	Beltran-Navarro et al., 2012	n=58 14- to 18-Month-Old Infants.	Significant deficit in motor and language performance at 14–18 months of age among a group of infants with chronic ID compared to those who were IS at both six and 14–18 months of age. No difference in cognitive scores were seen.

Micro-nutrients	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Iron	Longitudinal	China	Santos et al., 2018	n=1194 Infants (9 Months of Age).	Infants with either prenatal or postnatal ID performed worse on gross motor tasks at nine months of age, than infants who were IS in either or both periods.
	Cross-Sectional	Rural China	Luo et al., 2015	n = 1808 Infants Aged 6–12 Months.	Infants with lower haemoglobin counts were significantly more likely to be delayed in both their cognitive and psychomotor development .
	RCT	India	Scott et al., 2018	n=140 Boys and Girls Aged 12-16 Years assigned to Consume Iron-Biofortified [Fe = 86 Parts Per Million (ppm)] or Conventional (Fe = 21–52 ppm) Pearl Millet.	Consuming Iron-Biofortified Pearl Millet improves Iron status and some measures of cognitive performance in Indian adolescents.
	Prospective Cohort	West Africa	Mireku et al., 2016	n=636 Mother-Singleton Child Pairs.	No difference in learning observed in infants at 12 months of age born to mothers who were Iron deficient (ID) versus those who were Iron sufficient (IS). No association between maternal Iron status (ID vs. IS) and infant motor development at 12 months of age was seen.
	Longitudinal	China	Armony-Sivan et al., 2016	n=80 Pregnant Women with Subsequent Offspring	Greater brain activation in the right hemisphere in infants who were ID at both birth and 9 months.
	Prospective Community-Based Study	Vietnam	Tran et al., 2014	n= 418 Pregnant Mother-Infant Pairs.	Motor scores were lower among infants born to mothers with Anaemia in late pregnancy, which was in turn associated with ID earlier in pregnancy. Maternal ID in pregnancy was not associated with motor skills at six months of age.

Table 5: Characteristics of Human Studies on the Effect of Mineral Intakes on Cognition

Micro-nutrients	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Iodine	Longitudinal	Netherlands	Finken et al., 2013	n=1765 Healthy 5-6 Year-Old Children.	Lower maternal free T4 concentration at the end of the first trimester predicted slower response speed and decreased stability in response speed in offspring at 5 to 6 years of age.
	RCT	Spain	Santiago et al., 2013	n=102 Infants Aged 6-18 Months.	No significant differences between the groups for motor and psychomotor development index scores at 6-18 months.
	RCT	Australia	Zhou et al., 2015	n=53 Infants Aged 18 Months..	No significant difference observed between the intervention compared to the control group for child cognition, language and motor skills at 18 months of age.
	Longitudinal	UK	Bath et al., 2013	n=1040 First-Trimester Pregnant Women (Singleton Pregnancy).	Children of women with low Iodine-to-Creatinine Ratio were more likely to have scores in the lowest quartile for verbal IQ, reading accuracy and reading comprehension.
	Longitudinal Follow-Up of a Cohort	Australia	Hynes et al., 2013	n=228 Offspring Followed-Up at 9 Years.	Children whose mothers had a Low Urinary Iodine Concentration had reductions of 10% in spelling, 7.6% in grammar, and 5.7% in English-literacy.
	Population-based Birth Cohort	Spain	Julvez et al., 2013	n=1761 Mother-Child Pairs.	Low free Thyroxine Levels were associated with a decrease of mental scores. No association between Thyrotropin Levels and mental scores or Psychomotor scores.
	Cohort	Norway	Abel et al., 2017	n=48,297 Mother-Child Pairs.	Low maternal Iodine intake during pregnancy was associated with symptoms of child language delay, behaviour problems, and reduced fine motor skills at 3 Years of age. The results showed no evidence of a protective effect of Iodine supplementation during pregnancy.
	Randomized, Double-Blind, Placebo Controlled Trial	India and Thailalnd	Gowachirapant et al., 2017	n=832 Pregnant Women and their Subsequent Offspring.	Daily Iodine supplementation in mildly Iodine-deficient pregnant women had no effect on child neurodevelopment at age 5–6 years.

Micro-nutrients	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Zinc	Longitudinal	Nepal	Siegel et al., 2011	n=367 Infants who were given Daily Supplementation with 5 mg of Zinc, 6.25 mg of Iron with 25 µg of Folic acid, or Zinc-Iron-Folic Acid, or Placebo.	Neither the combined nor the individual micronutrient supplements improved performance in five indicators of information processing.
	Review	NA	Gogia and Sachdev, 2012	n=2134 infants and children.	There is no convincing evidence that Zinc supplementation to infants or children results in improved motor or mental development.
	Follow-Up of a RCT	Thailand	Pongcharoen et al., 2011	n=560 Children Aged 9 Years who received Daily Iron, Zinc, Iron Plus Zinc, or a Placebo at 4–6 Months of Age for 6 Months.	Supplementation with Iron or Zinc or both during infancy does not lead to long-term cognitive improvement in 9-Years-old children.
	RCT	Nepal	Surkan et al., 2012	n=569 Rural Infants and Children Aged 4–17 Months.	Zinc supplementation confers a beneficial effect on the rate of head growth in infants.
	RCT	India	Mathur and Agarwal., 2015	n=100 Preterm Neonates.	Zinc supplementation in preterm breastfed infants (till 3-month corrected age) improves alertness and attention patterns.
	RCT	Tanzania	Locks et al., 2017	n=2400 Infants were Randomized to Zinc (Zn), Multivitamins (MV), Zinc and Multivitamins (Zn + MV) Or placebo at 6 Weeks of Age. n=247 Children Underwent Developmental Assessment.	Neither daily Zinc nor Multivitamin (Vitamins B-Complex, C, and E) supplementation led to improvements in any of the developmental domains assessed.
	RCT	Peru	Colombo et al., 2014	n=248 Infants who were Randomly Assigned to be Administered a Daily Liquid Supplement containing 10 mg/d of Zinc, 10 mg/d of Iron, and 0.5 mg/d of copper, or an Identical Daily Liquid Supplement containing only 10 mg/d of Iron and 0.5 mg/d of Copper at 6 Months of Age.	Zinc was found to be supportive in sustaining normative neurodevelopment in the first 2 years of life.
	Systematic Review and Meta-Analysis	NA	Sajedi et al., 2020	n=11,559 Children Aged 0-5 Years Old	Studies did not show the efficacy of zinc with or without iron co-supplementation on child mental and motor development up to 9 years old age

Table 6: Observational Human Studies on the Effects of Consumption of Animal Foods and Dairy Products on Cognition

Food Group	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Animal Foods					
Fish	Cross-Sectional	Greece	Anastasiou et al., 2017	n = 1864 (41% Men) Mean Age: 73.0 Years Elderly .	Fish consumption was associated with lower risk of dementia but not with global cognition.
		Poland	Bajerska et al., 2014	n = 87 (35% Men) Age: 70.0 Years Elderly >60 Years.	Better attention, Visual memory, Executive function, lower risk of MCI. No association with global cognition was seen.
		Australia	Crichton et al., 2013	n = 1183 (36% Men) Age: 50.6 Years Adults from 40 to 65 Years.	No association with global cognition was seen.
		Spain	Valls-Pedret et al., 2012	n= 447 (48% Men) Age: 66.9 Years Community Dwelling People ⩾55 Years.	Episodic verbal memory, working memory.
	Longitudinal	US	Bhushan et al., 2018	n = 27,842 (100% Men) Age: 51 Years Male Health Professionals.	Better subjective cognitive function and less cognitive decline.
		Sweden	Shakersain et al., 2018	n = 2223 (39% Men) Age: 69.5 Years Community Residents.	
		Australia	Cherbuin and Anstey, 2012	n = 1528 (± 49% Men) Age: 60–64 Years.	Increased risk of MCI, mild cognitive disorder, and cognitive decline.
		China	Qin et al., 2015	n = 1650 (± 50% Men) Age ⩾55 Years Elderly.	Less cognitive decline.
Meat	Cross-Sectional	Spain	Valls-Pedret et al., 2012	n= 447 (48% Men) Age: 66.9 Years Community Dwelling People ⩾55 Years.	Worse cognitive function.
	Longitudinal	Sweden	Titova et al., 2013	n = 194 (52% Men) Age: 70.1 Years.	
Red Meat	Cross-Sectional	Poland	Bajerska et al., 2014	n = 87 (35% Men) Age: 70.0 Years Elderly >60 Years.	Worse executive function.
Red and Processed Meat	Longitudinal	US	Bhushan et al., 2018	n = 27,842 (100% Men) Age: 51 Years Male Health Professionals.	No association was seen with cognitive decline.
	Longitudinal	Sweden	Shakersain et al., 2018	n = 2223 (39% Men) Age: 69.5 Years, Community Residents.	

Food Group	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Red and Processed Meat	Longitudinal	China	Qin et al., 2015	n = 1650 (± 50% Men) Age ⩾55 Years Elderly.	No association was seen with cognitive decline.
	Longitudinal	US	Samieri et al., 2013a	n = 16,058 (100% Women) Mean Age: 74.3 Years Women from the Nurses' Health Study ⩾70 Years.	
	Longitudinal	US	Samieri et al., 2013b	n = 6174 (100% Women) Age: 72 Years Subset of Participants from the Women's Health Study Aged ⩾65 Years.	
	Longitudinal	US	Wengreen et al., 2013	n = 3580 (± 43% Men) Age ⩾65 Years, Non-Hispanic White.	
Poultry	Cross-Sectional	Greece	Anastasiou et al., 2017	n = 1864 (41% Men) Mean Age: 73.0 Years Elderly.	No association with cognitive function.
	Cross-Sectional	Poland	Bajerska et al., 2014	n = 87 (35% Men) Age: 70.0 Years, Elderly >60 Years.	
	Cross-Sectional	Australia	Crichton et al., 2013	n = 1183 (36% Men) Age: 50.6 Years, Adults from 40 to 65 Years.	
	Longitudinal	Sweden	Shakersain et al., 2018	n = 2223 (39% Men), Age: 69.5 Years, Community Residents.	Less cognitive decline.
Dairy					
Dairy	Cross-Sectional	Poland	Bajerska et al., 2014	n = 87 (35% Men), Age: 70.0 Years Elderly >60 Years.	Worse cognitive function on at least some cognitive domains.
	Longitudinal	Sweden	Shakersain et al., 2018	n = 2223 (39% Men), Age: 69.5 Years Community Residents.	
	Longitudinal	Australia	Cherbuin and Anstey, 2012	n = 1528 (± 49% Men) Age: 60–64 Years.	Higher risk of MCI and mild neurocognitive disorder.

Food Group	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Cheese	Longitudinal	Australia	Hosking et al., 2019	n= 1220 (50% Men) Age: 60–64 Years Elderly.	No association with cognitive impairment.
High-Fat Milk	Longitudinal	Sweden	Shakersain et al., 2018	n = 2223 (39% Men) Age: 69.5 Years, Community Residents.	Associated with cognitive decline.
Margarine					
Ice-Cream					No association with cognitive decline.

Table 7: Observational Human Studies on the Effects of Consumption of Plant-Based Foods on Cognition

Food Group	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Plant-Based Foods					
Plant Foods	Cross-Sectional	Australia	Crichton et al., 2013	n = 1183 (36% Men) Age: 50.6 Years, Adults from 40 to 65 Years.	No association was noted with self-reported cognitive function.
	Cross-Sectional	Poland	Bajerska et al., 2014	n = 87 (35% Men) Age: 70.0 Years Elderly >60 Years.	Better cognitive function. Better visual memory.
	Longitudinal	US	Bhushan et al., 2018	n = 27,842 (100% Men) Age: 51 Years, Male Health Professionals.	Better subjective cognitive function and less cognitive decline.
	Longitudinal	Greece	Trichopoulou et al., 2015	n= 401 (36% men), Age >65 Years Elderly.	
	Longitudinal	US	Samieri et al., 2013a	n = 16,058 (100% Women) Mean Age: 74.3 Years Women from the Nurses' Health Study ⩾70 Years.	
Vegetable Consumption	Longitudinal	Australia	Cherbuin and Anstey, 2012	n = 1528 (± 49% Men) Age: 60–64 Years.	Higher risk of MCI. But not of mild cognitive disorder/ cognitive decline.
Green Leafy Vegetable	Longitudinal	Australia	Hosking et al., 2019	n= 1220 (50% Men), Age: 60–64 Years Elderly.	GLV intake did not lower the risk of cognitive impairment.

Food Group	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Olive Oil	Cross-Sectional	Poland	Bajerska et al., 2014	n = 87 (35% Men) Age: 70.0 Years Elderly .	Better cognitive function or less cognitive decline.
	Cross-Sectional	Spain	Valls-Pedret et al., 2012	n= 447 (48% Men) Age: 66.9 Years Community Dwelling People.	
	Longitudinal	Spain	Galbete et al., 2015	n = 823 (71% Men) Age: 61.9 Years Spanish University Graduates.	
Walnuts	Cross-Sectional	Spain	Valls-Pedret et al., 2012	n= 447 (48% Men) Age: 66.9 Years Community Dwelling People.	Better cognitive function.
	Longitudinal	Australa	Hosking et al., 2019	n= 1220 (50% Men) Age: 60–64 Years Elderly.	Better cognitive function and a lower risk of cognitive impairment.
	Longitudinal	US	Bhushan et al., 2018	n = 27,842 (100% Men) Age: 51 Years Male Health Professionals.	
	Longitudinal	US	Wengreen et al., 2013	n = 3580 (± 43% Men) Age ⩾65 Years Non-Hispanic White.	
Legume	Longitudinal	US	Wengreen et al., 2013	n = 3580 (± 43% Men) Age ⩾65 Years Non-Hispanic White.	Better cognitive function.
Fruit	Cross-Sectional	Spain	Valls-Pedret et al., 2012	n= 447 (48% Men) Age: 66.9 Years, Community Dwelling, People ⩾55 Years	No association was seen with cognitive function.
	Cross-Sectional	Greece	Anastasiou et al., 2017	n = 1864 (41% Men) Mean Age: 73.0 Years Elderly.	
	Cross-Sectional	Poland	Bajerska et al., 2014	n = 87 (35% Men) Age: 70.0 Years. Elderly > 60 Years	

Food Group	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Berries	Longitudinal	Australia	Hosking et al., 2019	n= 1220 (50% Men) Age: 60–64 Years Elderly	No association with cognitive impairment was noted.
Potatoes	Cross-Sectional	Greece	Anastasiou et al., 2017	n = 1864 (41% Men) Mean Age: 73.0 Years Elderly.	No effect on cognitive function.
	Cross-Sectional	Poland	Bajerska et al., 2014	n = 87 (35% Men) Age: 70.0 Years, Elderly >60 Years.	
	Longitudinal	Sweden	Titova et al., 2013	n = 194 (52% Men), Age: 70.1 Years.	
Cereals and Grains					
Refined Cereals	Cross-Sectional	Spain	Valls-Pedret et al., 2012	n= 447 (48% Men) Age: 66.9 Years Community Dwelling People.	Worse cognitive function.
	Longitudinal	Australia	Cherbuin and Anstey, 2012	n = 1528 (± 49% Men) Age: 60–64 Years.	
Non-Refined Cereals	Cross-Sectional	Greece	Anastasiou et al., 2017	n = 1864 (41% men) Age: Elderly >64 Years.	Better cognitive function. .
Refined Grains	Longitudinal	Sweden	Shakersain et al., 2018	n = 2223 (39% Men) Age: 69.5 Years Community Residents.	Cognitive decline.
Whole Grains	Longitudinal	US	Samieri et al., 2013b	n = 6174 (100% Women) Age: 72 Years (Subset of Participants from the Women's Health Study).	Better average performance on at least some cognitive domains.
	Longitudinal	US	Wengreen et al., 2013	n = 3580 (± 43% Men) Age ⩾65 Years, Non-Hispanic White.	

Table 8: Observational Human Studies on the Effect of Consumption of Alcohol, Beverages and other Processed Foods on Cognition

Food Group	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Alcohol					
Alcohol	Cross-Sectional & Longitudinal	US	Bhushan et al., 2018	n = 27,842 (100% Men) Age: 51 Years Male Health Professionals.	No association noted with cognitive function.
		Italy	Tanaka et al., 2018	n= 832; Age: 75.4 Years (44% Men) Older Adults.	
		Greece	Anastasiou et al., 2017	n = 1864 (41% Men) Age: 73.0 Years Elderly >64 Years.	
		China	Qin et al., 2015	n = 1650 (± 50% Men) Age ⩾55 Years Elderly.	
		Poland	Bajerska et al., 2014	n = 87 (35% Men) Elderly >60 Years.	
Wine	Cross-Sectional	Spain	Valls-Pedret et al., 2012	n= 447 (48% Men) Age: 66.9 Years Community Dwelling People ⩾55 Years.	Better global cognition and less cognitive decline.
Spirits/ Beers	Longitudinal	Sweden	Shakersain et al., 2018	n = 2223 (39% Men) Age: 69.5 Years Community Residents.	No association with cognitive decline.

Food group	Study Design	Country	Authors & Year	Sample (Sex, Size and Age)	Results
Others					
Sugar/ Fruit Juice	Longitudinal	Sweden	Shakersain et al., 2018	n = 2223 (39% Men) Age: 69.5 Years Community Residents.	No association with more cognitive decline.
Sweetened Beverages	Longitudinal	US	Wengreen et al., 2013	n = 3580 (± 43% Men) Age ⩾65 Years Mainly Non-Hispanic White.	No association with cognitive decline.
Sodium	Longitudinal				No association with cognitive decline or cognitive impairment.
Processed and Fast/Fried Food	Longitudinal	Australia	Hosking et al., 2019	n= 1220 (50% Men) Age: 60–64 Years Elderly.	
Sweets and Pastries	Longitudinal				
Animal-Source Cooking Fat	Longitudinal	China	Qin et al., 2015	n = 1650 (± 50% Men) Age ⩾55 Years Elderly.	

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