VILNIUS UNIVERSITY

MEDICAL FACULTY

The Final thesis

The relationship between diet and mental health in children and adolescents

Gal Zim, Medicine sixth year student, group 4

Department/ Clinic (where the defense procedure is taking place)

Institute of Clinical Medicine Clinic of Children's Diseases

Supervisor: prof. Vaidotas Urbonas ____________________

(signature)

Consultant (if applicable) ____________________

(signature)

The Head of Department/Clinic: prof. Augustina Jankauskienė ____________________

(signature)

Registration day at Department/Clinic______________

(filled in by technical assistant of Department/Clinic)

Registration n.______________

(filled in by technical assistant of Department/Clinic)

Email of the student: gal.zim@mf.stud.vu.lt

Contents

Abstract

This literature review is focusing on the link between nutrition consumption on the control of mental health disorders among children and adolescents. The main purpose of the thesis is to give a glimpse of the possible dietary effects on mental health disorders and conditions and how they may regulate some mental health patterns in this age population.

This work critically reviews international studies on the relationship between diet and mental health in children and adolescents that take stock of the current state of the art, in the field of medical studies. The literature search strategy sought to facilitate the undertaking of the newest and most relevant research on this topic. The majority of this thesis is based on the most relevant and available research literature from Pubmed/NCBI. Google scholar has been used as an essential tool, to begin with for a reviewed literature on the subject matter at hand. Within the largest medical databases of Pubmed/NCBI, the fundamental keywords listed below were used in order to find the most relevant and state-of-the-art research. All publications were critically analyzed, focusing on their content as well as the objectives and methodologies found to be of most interest to academic output on the subject of the relationship between diet and mental health in children and adolescents. A critical analysis was also carried out to identify the aspects that were the focus of the research and those that received less attention. For more specific information, terms and keywords of major mental health conditions were used together with the words:" children" or "adolescents" and the group of nutrients (e.g. "children depression lipids" or "adolescents anxiety carbohydrates"). This systematic procedure carried broader data of information and assisted in withholding missed pieces of information.

Many research articles were brought here in order to show the bloom and evolvement of this considered new research field related to mental health with nutrition.

6 groups of nutrition are to be assessed: carbohydrates, proteins, lipids, vitamins, minerals, and water. Children and adolescents are nowadays found to be in an increased rate of development of mental health conditions more than ever with life stress, world development and demands and are considered a more sensitive age group population, hence specialized care is necessary. Nutrition commonly tends to be neglected in this age group due to factors such as lack of security, self-confidence, poverty and emotional state. In the last two decades, the correlation idea between nutrition and mental state has significantly arisen. Some of the research articles and

studies here have given us a new variety of possibilities in the way of treating and controlling mental health in children and adolescents with the helpful effects of nutrition and diet. Controlling the mental health disorders and preventing deterioration in their patterns using diet may improve their condition and quality of life.

Keywords: nutrition, diet, children, adolescents, mental health, depression, anxiety, mood, behavior, food.

List of abbreviations

GBA	Gut-brain axis
MGB	Microbiota-gut-brain axis
CNS	Central nervous system
FAs	Fatty acids
ADHD	Attention deficit hyperactivity disorder
5-HTP	5 Hydroxytryptophan
GABA	Gamma-aminobutyric acid
MDD	Major depressive disorder
ENS	Enteric nervous system
Ach	Acetylcholine
AChR	Acetylcholine receptor
AchEIs	Acetylcholinesterase inhibitors
AChEs	Acetylcholinesterases
ASDs	Autism spectrum disorders
SFAs	Saturated FAs
MUFAs	Monounsaturated FAs
PUFAs	Polyunsaturated FAs
CCK	Cholecystokinin
EFAs	Essential fatty acids
ADH	Antidiuretic hormone
Vit	Vitamin

Introduction

The role of nutrition and diet in the development of psychiatric, neurological, and depressive disorders has become a recent research focus over the past decade (1).
The composition of the gut microbiota depends on an individual's genetic predisposition, age, nutrition, physical activity, environmental factors, stress, infection, other diseases, and use of medications (antibiotics, acid reducing medicines, etc.). This work is focusing on the importance of diet on mental health. Our nutrition has a tremendous impact on our microbiome composition. The gut-brain axis (GBA) and especially the microbiota-gut-brain axis (MGB) has a significant role in the evolution of neuropsychiatric diseases. The gut-brain axis is composed of the central nervous system (CNS, represented by the brain), the enteric nervous system, and the digestive system. It is involved in gut motility, secretion of hormones, and production of acid, bicarbonates, and mucus. When intestinal microorganisms are involved, they regulate the brain, behaviors, and stress responses. This form of communication is called the microbiota-gut-brain (MGB) axis (2). These systems communicate via bidirectional communication, emotional and cognitive centers of the brain are linked with peripheral intestinal functions (3).

Gut microbiota maintains a bidirectional interaction with the central nervous system through direct and indirect pathways. Gut microorganisms regulate the brain, behaviors, and stress responses, stress can alter the pattern of mucus secretion, which can have a profound impact on the proliferation of intestinal microorganisms. The interaction between microbiota and GBA appears to be bidirectional. Signaling occurs from gut-microbiota to brain and from the brain to gut-microbiota through neural, endocrine, immune, and antibody-mediated immunity links. Nowadays, we know there is a complex interaction between the host and its microorganisms. This interaction does not affect only digestion and utilization of energy, but also brain function and behavior (2).

Nutrition is a serious cofactor intertwined with human cognition, behavior, and emotions. Nutrients are compounds found in our food and drinks which are essential for our life and health supplying us with energy. The dietary intake patterns of the general population show a deficiency in many nutrients, especially essential vitamins, minerals, and omega-3 fatty acids (FAs). A notable feature of the diets of patients suffering from mental disorders is the severity of deficiency in these nutrients. Studies have indicated that daily supplements of vital nutrients are often effective in reducing patients' symptoms of mental disorders. This explains why nutrients are playing a vital role in the gut-brain axis (4).

This reviewed literature thesis deals with the relationship between the diet that children and adolescents consume and its impact on their mental health. The main goal is to give us a clue about the impact of nutrition on mental health in the population of children and adolescents and further on- the brain. Why does the food that we eat so important to our mental health? What could we learn from that? How can we better understand the development of mental health due to our nutrition?

This thesis is written based on chosen examples, studies and trials. Due to the enormous amount of nutrients in each group and limited paperwork, this document isn't able to include all the subdivisions of the nutrients that are vital for us.

This field in modern medicine is still developing, thus lacking information and further studies. The cornerstones of this work are Carbohydrates, proteins, lipids, vitamins, minerals, and water consumption, and they are the main ones to be evaluated in this new forward-looking research discipline.

Carbohydrates

Carbohydrates are found to affect mood and behavior (4). Carbohydrates are one of the three macronutrients in the human diet, along with protein and fat and play an important role in the structure and function of an organism (4,5). Carbohydrates act as a source of energy and are used as an energy reserve storage, help control blood glucose and insulin levels, participate in cholesterol and triglyceride metabolism, build important macromolecules such as RNA and DNA and assist with fermentation (5).

The classification of dietary carbohydrates is primarily based on chemical composition. Monosaccharides are the most basic, fundamental unit of carbohydrate (glucose, galactose, fructose, galactose). Disaccharides are compound sugars containing two monosaccharides (sucrose, lactose, maltose). Oligosaccharide, this polymer contains 3-10 monosaccharides and Polysaccharides, which are polymers that contain long chains of monosaccharides. Additionally, carbohydrates are divided into categories of simple and complex. Simple carbohydrates are one or two sugars (monosaccharides or disaccharides) easily utilized for energy, causing a rapid rise in blood sugar and insulin secretion from the pancreas. Simple carbohydrates appear in foods such as candies, carbonated beverages, fruit juice, corn syrup, honey, and table sugar. Complex carbohydrates are three or more sugars (oligosaccharides or polysaccharides), which longer time is taken for them to be digested and therefore have a more gradual effect on rising in blood sugar. They appear in foods such as apples, broccoli, lentils, spinach, unrefined whole grains, and brown rice. Starch and fiber are the main dietary of complex carbohydrates. Starches are polysaccharides that are produced by plants. They appear in foods such as potatoes, chickpeas, pasta, and wheat. Fibers are non-digestible complex carbohydrates that encourage the growth of healthy bacteria in the colon and ease defecation. They appear in foods such as bran, seeds, vegetables, meaty fruits, brown rice, and potato skins (5).

Initially, the digestion of these complex carbohydrates begins with salivary alpha-amylase while still in the mouth and while passing throughout the esophagus. Later on, salivary-amylase is deactivated by the acid pH of the stomach so that it remains active only as long as it is protected from this acidic environment. Inside the small intestine, pancreatic juice (which contains high bicarbonate concentration) enters the lumen through the sphincter of Oddi and begins to neutralize the gastric acid. Simultaneously, pancreatic-amylase reaches the lumen and actively continues to break down complex carbohydrates into oligosaccharides. Additional digestion is required before the absorption of the monosaccharide breakdown products of complex carbohydrates. They must be further broken down by the disaccharidases which are brush-border plasma membrane enzymes of intestinal epithelial cells (enterocytes-absorptive cells) that cleave one monosaccharide at a time from the oligosaccharides or convert disaccharides into monosaccharides. Once monosaccharides result from this digestion, the monosaccharides are taken up by the enterocytes (6).

Upon absorption of carbohydrates, glucose enters beta cells by GLUT2 receptor following a concentration gradient, it then undergoes metabolism and ATP is produced. This ATP binds a potassium channel which stimulates its closure. Potassium is no longer possible of leaving the membrane causing a building up of positive charges potassium ions within the cytosol of the betta cell which causes a depolarization of the cell. This depolarization causes calcium channels to open up which will allow calcium influx into the cytosol of the beta-cell. Calcium then will trigger insulin exocytosis from the beta cell granules into the blood. That way, insulin instructs the cells to open up and grant entry to glucose (7).

Concomitantly, insulin triggers the entry of tryptophan into the brain which is the building block of serotonin (4). This is important to mention as some most common sources of tryptophan are carbohydrates: oats, bananas, dried prunes, bread, and chocolate! (8). Consumption of low carbohydrates in the diet tends to precipitate depression since the production of serotonin that promotes the feeling of well-being is triggered by carbohydrate-rich foods (4). Plant-rich foods that are abundant in carbohydrates and fibers have been correlated with *Prevotella* species which play an important nutritional factor in human beings and certainly in children (9).

A new study in Australia has pinpointed that *Prevotella* species may predict a child's risk of future anxiety. *Prevotella* is a gram-negative bacterial genus that is more abundant amongst populations living in non-westernized environments. The study is the first one to show that children with a lower amount of *Prevotella* at age one are more likely to have anxiety-like behaviors. Researchers examined data from 201 children, analyzing poo samples at one, six, and 12 months of age, then the behavioral outcome was measured at two years of age. They found that children with a lower abundance of the bacteria *Prevotella* in their poo at 12 months of age had a higher prevalence of anxiety-like behaviors, including shyness, sadness, and an internal focus. These behaviors are indicators in which those children may be at higher risk of developing childhood anxiety (10). Beyond the effect of anxiety, there exists a popular theory claiming that sugar has an influence on children's behavior and increases psychomotor activity (11).

Another report has investigated the relationships between sleep and diet in 88 Australian children 6-13 years old. The data has shown that 30% of the children had sleep disturbance with significant relationships between ADHD (attention deficit hyperactivity disorder) symptoms, sleep disturbance, and diet. Parents who reported more sleep disturbance also reported a higher intake of carbohydrates, fats, and sugar in particular (12). Moreover, Iran study from 2012 showed a correlation between a high level of added sugar in the diet and the prevalence of attention-deficit hyperactivity disorder (13).

The correlation between the level of added sugar and sodium intake and the prevalence of externalizing behaviors among pre-school children was also assessed and proved that such a correlation exists, however, it differs depending on sex. Girls who presented behavior disorders had higher sodium levels per 1000 kcal and lower energy from added sugars than girls without such disorders. On the other hand, boys who presented externalizing behaviors had a higher dietary intake of added sugars and less sodium than others (14).

Although, the theory that indicates the relationship between high intake of sugars and hyperactive behaviors was investigated multiple times, it has not been confirmed in scientific research. Even though no absolute scientific foundations are limiting the intake of simple sugars and eating instead polysaccharides to improve behavior and cognitive functions, it's coherent with healthy diet recommendations and should be recommended for children and adolescents (11).

Proteins

Proteins are made up of amino acids and are important building blocks of life. 11 amino acids are manufactured in the body itself and the general held thought is that there are nine essential amino acids, including phenylalanine, valine, tryptophan, threonine, isoleucine, methionine, histidine, leucine, and lysine. The essential amino acids need to be supplied from an exogenous diet since the human body lacks the metabolic pathways which are required to synthesize these amino acids (4,15).

A great quality protein diet has to contain all the essential amino acids. The protein intake as well as the individual amino acids consumption can affect mental health and brain functioning. Amino acids have also been found to reduce symptoms as they are converted to neurotransmitters (many of the neurotransmitters in the brain are made of amino acids). Neurotransmitters then in turn alleviate depression and some other mental health disorders. Some good examples are the neurotransmitter of dopamine, which is made up of the amino acid tyrosine, and the neurotransmitter serotonin which is made from tryptophan. Lacking any of these amino acids will lead to the insufficient synthesis of these key neurotransmitters. This condition is associated with low mood and even aggression (16).

One research has shown that L-tryptophan's role in brain serotonin synthesis is an important factor involved in mood, behavior, and cognition. The brain of the child has a very limited storage capacity for tryptophan, and the overall tryptophan concentration in the body is the lowest among all amino acids. Children need a constant supply of tryptophan reaching the brain so that serotonin levels will remain optimal (8).

Microbes within the gut especially *Bifidobacterium*, are capable of producing tryptophan, thus a normal level of *Bifidobacterium* in children and adolescents is vital for promoting a healthy microbial environment. Besides, studies have found that *Bifidobacterium* has some positive effects on stress-related diseases and the probiotic *Bifidobacterium infantis* may possess antidepressant properties (2).

During times of inadequate intake of essential amino acids, clinical symptoms may appear including depression, anxiety, insomnia, fatigue, weakness, and growth stunting among children and young. These deficiencies are usually present in poorer parts of the world in developing countries or also in elderly adults with inadequate care (16).

Usually, there are two sides to depression: feeling apathetic and unmotivated and feeling miserable. The most abundant biochemical theory describing the cause of these category feelings is a brain imbalance which appears in two families of neurotransmitters:

1) Serotonin-primarily influences mood
2) Dopamine, noradrenaline, and adrenaline-primarily influence motivation (16).

Fig.1. Nutrients that make mood-enhancing neurotransmitters

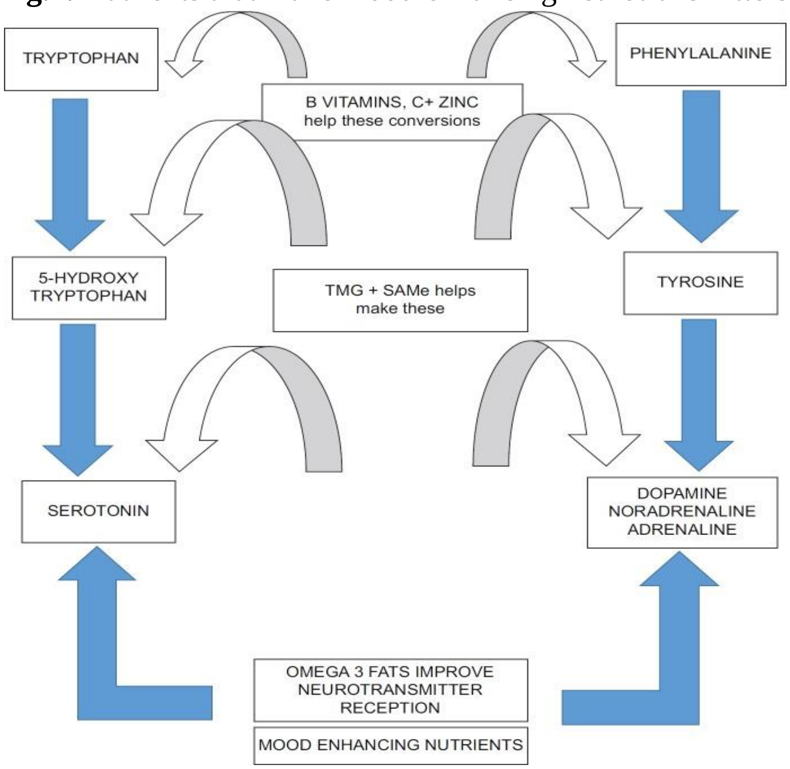

Figure 1 showing the nutrients that are essential for the production of serotonin, dopamine, adrenaline, and noradrenaline. Source: Adapted from Holford, 2003; Depression: the nutrition connection. Primary Care Mental Health 1: 9-16. (16).

If an individual suffers from low mood, feels tense and irritable, is tired most of the time, tends to eat emotionally, and has sleeping problems, then chances point the individual is probably short on serotonin (16).

Fig.2. Deficiency of neurotransmitters and their relationship with food.

Neurotransmitter	Effects of deficiency	Foods to avoid	Foods to consume
Acetylcholine	Deterioration of memory and imagination	Sugar	Organic/free-range eggs
	Fewer dreams	Deep-fried foods	Organic or wild fish - especially salmon, mackerel, sardines and fresh tuna
	Increased confusion, forgetfulness and disorganisation	Junk foods	
		Refined and processed foods	
		Cigarettes	
		Alcohol	
Serotonin	Low mood	Alcohol	Fish
	Difficulty sleeping		Fruits
	Feeling "disconnected"		Eggs
	Lacking joy		Avocado
			Wheatgerm
			Low-fat cheese
			Lean, organic poultry
Dopamine	Lacking drive, motivation and/or enthusiasm	Tea and coffee	Regular, balanced meals
	Crave stimulants	Caffeinated drinks and pills	Fruits and vegetables high in vitamin C
			Wheatgerm
			Fermented products
Gamma-Amino Butyric Acid (GABA)	Hard to relax	Sugar	Dark green vegetables
	Anxious about things	Alcohol	Seeds and nuts
	Irritable	Tea and Coffee	Potatoes
	Self-critical	Caffeinated drinks	Bananas
			Eggs

Figure 2 summarizes the effect of deficiency of the neurotransmitters, the foods that will make the deficiency worse, and those that will improve the symptoms. Source: Adapted from Holford, 2003; Depression: the nutrition connection. Primary Care Mental Health 1:9-16. (16).

One trial was taken place on 15 volunteers at Oxford University, UK. All 15 volunteers had a history of depression but were currently not depressed. They were given a nutritionally balanced drink that excluded tryptophan. Within seven hours from the consumption of the drink, 10 out of 15 participants noticed a worsening in their mood and started to show signs of depression. Later on, they were given the same drink, but this time with tryptophan added to the solution, their mood improved. The recommended dosage of 5 Hydroxy-tryptophan (5-HTP) is 100 mg 2-3 times per day for depression. Some other supplements also provide vitamins and minerals such as B12 and folic acid within them, which may be even more effective because these nutrients help to turn 5-HTP into serotonin (16).

Gamma-aminobutyric acid (GABA) is a non-protein amino acid that serves as the primary inhibitory neurotransmitter in the brain and as well as a major inhibitory neurotransmitter within the spinal cord. GABA is synthesized from the amino acid precursor glutamate by the enzyme glutamate decarboxylase, an enzyme that uses vitamin B6 (pyridoxine) as a cofactor element (17). low levels of GABA have been associated with various psychiatric illnesses such as generalized anxiety, schizophrenia, autism spectrum disorder, and major depressive disorder (MDD) (18). Due to its potential role as an inhibitory neurotransmitter, reduced levels of GABA would produce a feeling of anxiousness (18). A study from the USA took a place among kids (age range, 8–12 years) has shown that GABA concentration is reduced in children with ADHD (19). It has been found that certain probiotic strains contribute to the formation of GABA in the enteric nervous system (ENS). Specifically, bacteria from the strains *Lactobacillus* and *Bifidobacterium* were effective at increasing GABA concentrations in the ENS (20).

GABA is ubiquitously found among plants, where it can be synthesized from glutamate. Nowadays GABA is acknowledged for its analgesic, anti-anxiety, and hypotensive effects. Some researchers found that raw spinach of dry weight to be one of the highest contents of GABA, followed by potatoes, sweet potatoes, kale, and broccoli. Mushrooms such as shiitake type and chestnut also showed a significant amount of GABA (21).

Another essential amino acid to mention here is Lysine which is low in wheat and its products. A prolonged inadequate lysine diet in experimental animals increases stress-induced anxiety. A randomized, 3-month, double-blind study tested whether lysine fortification of wheat reduces anxiety and stress response in family members of poor Syrian communities whose diet staple was wheat-based. Lysine-fortification reduced plasma cortisol response in females, as well as sympathetic arousal in males as measured by skin conductance. These results suggest that some stress responses in economically weak populations consuming cereal-based diets can be improved with lysine fortification. Dietary inadequacy of an essential amino acid leads to signs of nonspecific protein deficiency such as reduced resistance to disease, lowered blood proteins, and stunting in children (22).

In general, amino acids in foods are rarely excessive or unbalanced. A vegetarian diet requires attention to amino acids that may be insufficient or unbalanced in some sorts of food. Methionine and tryptophan are found in grains complement while lysine and isoleucine are found in legumes. Tryptophan doses of at least 1 gram, mildly help insomniac patients fall asleep faster and wake up less frequently (23).

Acetylcholine (Ach) is a neurotransmitter that has a wide variety of functions in the brain and other organ systems of the body. Acetylcholine is not a protein like neurochemical, and isn't derived from any amino acid but needs to be mentioned here since this neurotransmitter is mainly found in protein-rich foods, and because of its significance in mood regulation. Acetylcholine also takes part in the gut-brain axis. In the gastrointestinal system, Ach works through stimulation of the vagus nerve, the tone and amplitude of contractions, secretory activity of the stomach and intestine, and the release of sphincters. Within the brain, Ach is involved in memory, motivation, arousal, and attention. Ach derives from two constituents, choline, and an acetyl group (ester of acetic acid which is derived from the coenzyme acetyl-CoA).

Over the last 50 years, clinical studies suggesting that increases in central acetylcholine may lead to depressed mood. Evidence has continued to accumulate suggesting that the cholinergic system plays an important role in mood regulation as well. The earliest observations of a potential link between acetylcholine and depression were based on clinical observations of the effects of ACh receptor (AChR) agonists, which activate AChRs, and acetylcholinesterase inhibitors (AChEIs), which prevent the breakdown of ACh by acetylcholinesterases (AChEs). AChEIs compose a class of insecticides used in agriculture, and nerve agents used in times of war (24).

Three-day food records were analyzed for 288 children with autism spectrum disorders (ASDs) who participated in the national Autism Intervention Research Network for Physical Health (AIR-P) Study on diet and nutrition in children with autism. Plasma concentrations of choline were measured in a subgroup of 35 children with ASDs and 32 age-matched control children. The results indicated that 60–93% of children with ASDs were consuming less than the recommended adequate intake for choline. Strong positive correlations were found between dietary intake and plasma concentrations of choline in autistic children as well as lower plasma concentrations compared to the control group. We conclude that choline intake is inadequate in a significant subgroup of children with ASDs and is reflected in lower plasma levels (25).

Choline is naturally present in foods such as egg yolks, liver, beef, chicken, fish, milk, seeds of various vegetables, and legumes (24,25). Inadequate intake of choline may contribute to the metabolic abnormalities observed in many children with autism and warrants attention in nutritional counseling (25).

Lipids

Lipids are a group of ubiquitous and diverse compounds which have many key biological functions in our body. Lipids are acting as structural components of cell membranes, serve as energy storage sources, participate in signaling pathways, provide insulation to cells, aid in the absorption of fat-soluble vitamins, and even help to protect the skin (26,27).

Not only, but the brain is one of the organs with the highest level of lipids. It has been estimated that grey matter contains 50% FAs (about 33% belong to the omega-3 family), hence are needed to be supplied through diet as the human body cannot produce it on its own (4).

Lipids comprise an extremely heterogeneous collection of molecules from a structural and functional standpoint, thus, it is not surprising that there are significant differences in the organization of classification schemes (26).

Dietary lipids comprise FAs and cholesterol. FAs can be free (found in butter, oils, milk) or esterified with glycerol forming triacylglycerols and other complex lipids (phospholipids, glycolipids, and glycoproteins). FAs differ by the length of the carbon chains (which influence the physicochemical properties), and for the absence or the presence of one or more double bonds. Based on this second characteristic, there are 3 main classes: saturated FAs (SFAs), monounsaturated FAs (MUFAs), and polyunsaturated FAs (PUFAs). PUFAs include two essential groups, omega-3 and omega-6 FAs, which have to be obtained through the diet because they cannot be synthesized in human beings. Among omega-3 FAs, linolenic acid is most prevalent in plants (flaxseed, canola, soybean, nuts, walnuts, chia seeds, etc.), while eicosapentaenoic acid and docosahexaenoic acid are present mostly in fish, seafood, and marine algae. Among omega-6 FAs, linoleic acid is provided by seed oils, soybean, nuts, and cereals, while arachidonic acid is found in poultry and eggs (28).

Lipids are fatty, waxy, or oily compounds that are soluble in organic solvents and insoluble in polar solvents such as water. Types of lipids include fats and oils (triglycerides), phospholipids, waxes, and steroids.

Fats and oils are esters made up of glycerol molecule and 3 FAs. Fatty acid double bonds can either be cis or trans, creating many different types of FAs. Triglycerides store energy, provide insulation to cells, and aid in the absorption of fat-soluble vitamins. Fats are normally solid at room temperature, while oils are generally liquid.

Phospholipids are an essential component of the cell membrane. The amphipathic structure is typically made of a glycerol backbone, 2 fatty acid tails (hydrophobic), and a phosphate group (hydrophilic). In the cell membrane, phospholipids are arranged in a bilayer manner, providing cell protection and serving as a barrier to certain molecules. The hydrophilic part is faced outward and the hydrophobic part facing inward. That specific arrangement helps monitor which molecules can enter and exit the cell. Nonpolar molecules and small polar molecules, such as water and oxygen, can easily diffuse in and outside the cell. Large, polar molecules such as glucose aren't able to pass freely so the help of transport proteins is needed.

Waxes are esters made of long-chain alcohol and a fatty acid providing protection, especially to plants in which wax covers the leaves of plants. In humans, earwax helps protect the skin of the ear canal.

The steroids class has a structure of 4 fused rings. One important type of steroid is cholesterol. Cholesterol is produced in the liver and used as a precursor to other steroid hormones, such as estrogen, testosterone, and cortisol (27).

Both cholesterol and triglycerides are nonpolar lipid molecules. Therefore, they must travel in the polar plasma with the help of lipoprotein particles.

The transport of plasma lipids involves exogenous and endogenous routes. The exogenous path includes the transport of dietary triglycerides and cholesterol from the small intestine. In the small intestine, triglycerides are broken down with the help of enzymes and bile acids. Digestive products from this breakdown (such as free fatty acids) trigger the release of the Cholecystokinin

(CCK) hormone by the duodenum. CCK activity stimulates bile release into the small intestine, and further on triggers the pancreas to release digestive enzymes into the intestine. Pancreatic lipase breaks down triglycerides to produce free FAs and monoacylglycerol, which are then absorbed by the intestinal mucosal cells. FAs are absorbed through the intestinal mucosal villi and enter the bloodstream through capillaries, reach the portal vein, and are taken to the liver with the help of lipid carrier proteins to be used for energy. Longer-chain FAs, however, are absorbed by the intestinal mucosa from the lumen, where they are re-esterified to form triglycerides and are incorporated into chylomicrons. Chylomicrons are then released into intestinal lymph, secreted into the blood through the lymphatic thoracic duct, and attached to capillary walls in adipose and skeletal muscle tissues. At the attachment points, chylomicrons interact with the enzyme lipoprotein lipase, leading to the breakdown of triglyceride core, and free FAs are then released. The FAs penetrate through the capillary endothelial cells and are either stored in adipose cells or oxidized in skeletal muscle cells (27).

The endogenous route is when cholesterol and triglycerides travel from the liver and other non-intestinal tissues into circulation. The liver produces triglycerides from carbohydrates and free FAs. These triglycerides are then released into plasma in the core of VLDL which then interact with lipoprotein lipase in tissue capillaries, causing triglyceride core hydrolysis and free FAs liberation. Some remnant particles are taken out of the plasma and bind to the hepatic cells. The rest of the remnants transform into LDL particles, providing cholesterol to the cells.

When energy is needed, fat can also be broken down for energy utilization. Glucagon (which is released during fasting) or epinephrine (which is released during exercise) activates adipose triglyceride lipase, hormone-sensitive lipase, and monoglyceride lipase for the liberation of FAs. These FAs can then be used for energy by most tissues (27).

In recent years, many studies helped to draw a line between the relationship between lipids and mental health. It is advised to recognize the essential FAs in the human body and among children and adolescents.

The most important fats are those that the body cannot make and thus must come from the food we eat. These essential fatty acids (EFAs) are based on linoleic acid (omega-6 group) and alpha-linolenic acid (omega-3 group). We need both groups of EFAs to survive (29).

EFAs play a major role in brain development and brain functioning. The omega-3 series member's docosahexaenoic acid and eicosapentaenoic acid provide fluidity to the cell membrane and facilitate processes including neurotransmission and ion channel flow. There is no evidence that FAs monotherapy has a mood-elevating effect, with a possible exception for childhood depression. It is thought that omega-3 deficiency during the fetal and postnatal period may have a long-term effect at various levels and on top of that, there are indications that omega-3 has a prophylactic effect on perinatal depression (30).

FAs especially omega-3/6 may be efficient for controlling symptoms of some psychiatric disorders among children. A systematic review of 16 randomized controlled trials was undertaken with a total of 1514 children and young people with ADHD who were allocated to take an omega-3/6 intervention or a placebo. 13/16 studies reported results of favorable benefits on ADHD symptoms including improvements in hyperactivity, impulsivity, attention, visual learning, word reading, and working/short-term memory (31).

Another research that took a place in Slovakia has strengthened the link between depression and intake of omega-3 FAs. This study was the first to report that omega-3 FAs, increase large HDL subfractions after only 12 weeks of supplementation and decrease small HDL subfractions (large HDL subfractions are associated with reduced severity of depressive symptoms in depressed children and small HDL subfractions with worsening) (32).

Omega-3 FAs have been shown to attenuate the persistent elevation of the stress response in animal models and humans with depressive features. There are pieces of evidence that support an altered immune modulation in the pathophysiology of depression. Chronic stress, elicits a neuroinflammatory response, releasing inflammatory mediators, such as interleukin-1β and tumor necrosis factor-α (TNF-α), these two cytokines are inhibited by omega-3 FAs. Given the link between depression and an increase in pro-inflammatory cytokines production, this inhibition might explain some of the antidepressant effects of omega-3 FAs. Chronic stress also changes the immune system's activation in the periphery, which may explain the state of chronic inflammation observed in depressed patients. Moreover, cytokines also decrease the availability of neurotransmitter precursor, and by this, inhibit neurotransmitter metabolism which might be crucial in the pathogenesis of mood disorders (33).

Epidemiological studies have demonstrated a positive association between omega-3 deficits and mood disorders. As for treatment, there is convincing evidence that adding omega-3 FAs to standard antidepressant pharmacotherapy results in improved mood (30).

Several randomized controlled trials conducted in minors have shown at least some encouraging results. In a small study including 20 depressed children 6-12 years old, omega-3 FAs supplementation showed a large advantage over placebo. Though, given the small sample size, these results need to be further interpreted with caution. A large study to date included 72 youth with pediatric depression aged 7-14 years who underwent omega-3 monotherapy, individual-family psychoeducational psychotherapy, or combinations. Respectively, for a trial duration of 12 weeks, the omega-3 treatment showed a small to medium effect compared to the placebo. Another study included 14 adolescents with resistant MDD. For 10 weeks, half of them received a very high dose of 16.2 g omega-3 FAs per day and the other half received a low dose of 2.4 g per day. Among the high-dose group, 100% of adolescents showed symptoms of remission compared to the 40% in the low-dose group. In contrast to this study though, no beneficial effects of omega-3 FAs were found in another study trial including 51 adolescents with MDD who were treated for 10 weeks. Preliminary data point toward the beneficial effects of omega-3 FAs on pediatric depression but large-scale studies are needed for validating these results (33).

Vitamins

Vitamins are essential micronutrients of the diet that are not synthesized by humans. Some vitamins are synthesized in the human body to some extent, but in amounts that are insufficient to support health, hence we have to get vitamins through our diet. Vitamins are mostly classified as water-soluble or fat-soluble. The fat-soluble vitamins include A, D, E, and K. The water-soluble vitamins are C and B complex group (include: niacin, riboflavin, biotin, pantothenic acid, pyridoxine, thiamine, folate, and cobalamin) (34,35)

Fat-soluble vitamins, despite their structural differences, are absorbed and transported similarly due to their low solubility in hydrophilic media. The body absorbs fat-soluble vitamins into newly forming micelles in the small intestine (micelles are lipid clusters that contain hydrophobic groups internally and hydrophilic groups externally). This process relies on the bile and pancreatic secretion of enzymes. After absorption into enterocytes, fat-soluble vitamins become packaged into chylomicrons, which are then secreted into the lymphatic system entering the bloodstream. Chylomicrons are metabolized by lipoprotein lipase, which causes the release of fat-soluble vitamins into tissues for use and storage. Fat-soluble vitamins are retained by the body for a longer time than water-soluble vitamins due to the fact they are stored in tissue. Fat-soluble vitamins play integral roles in a variety of physiological processes such as vision, bone health, immune function, and coagulation. Rich sources of fat-soluble vitamins Include Egg yolk, milk, liver, cheese, butter, and plant sources including dark green leafy vegetables, carrots, squash, mangoes, etc.' (A). Salmon, tuna, and mackerel (D), vegetable oils, seeds, nuts, and whole grains (E), green leafy vegetables, cabbage, and cauliflower (K) (34).

Vit. B complex and vitamin C are ubiquitous foods, especially vegetables and fruits, as well as dairy, meat, legumes, peas, liver, eggs, and fortified grains and cereals. Not only serving as cofactors in biochemical reactions, but B complex vitamins are also vital for normal body growth and development, healthy skin, the proper function of nerves and the heart, and red blood cell formation. Vit. C (ascorbic acid, ascorbate) is needed for collagen growth, wound healing, bone formation, enhancing immunity, iron absorption, blood vessel strengthening, and even serving as an antioxidant. Water-soluble vitamins dissolve in water upon entering the body, thus, humans cannot store excess amounts of water-soluble vitamins. for later use. The deficiency of water-soluble vitamins results in a clinical syndrome that may result in severe morbidity and mortality. (35).

Vitamins were investigated in recent years due to their theories about influencing mental health among children. Many researchers claim certain vitamins are associated with several mental health problems and some vitamins are vital for reducing symptoms of mental health issues.

Retinol is a natural form of vitamin A and according to a recent study, serum retinol levels in children with ASD were significantly lower than in control children. Serotonin levels in children with ASD were higher than in control children as well, this is correlated with symptom severity of children with autism. After supplementation with vit. A, the children with ASD exhibited a significant improvement in autism symptoms. Serum retinol concentrations of children with ASD were significantly increased, and serotonin levels declined. These results indicate that vitA supplementation is a reasonable therapy at least for a subset of children with autism (36).

Vitamin D deficiency is also associated with ASD. There is an increasing amount of evidence pointing to the possibility that gestational and early childhood vit. D deficiency [25(OH)D < 40 ng/ml] cause some cases of autism. Children who are destined to become autistic have lower 25(OH)D levels at 3 months of gestation at birth and 8 years of age compared to their unaffected siblings. Two open-label trials found that high doses of vit. D improves core symptoms of autism in about 75% of autistic children. A few improvements were remarkable. The vit. D doses used in these children were 300 IU/kg/day up to a maximum of 5000 IU/day. The other study used 150,000 IU/month IM as well as 400 IU/day. These two trials were recently confirmed with a randomized controlled trial using 300 IU/kg/day with a maximum of 5000 IU/day and resulting in similar effects as the two open-label studies.

By the means of prevention, a recent small study showed vit. D supplementation during pregnancy (5000 IU/day), infancy and early childhood (1000 IU/day) significantly reduced the expected incidence of autism in mothers who already had one autistic child from 20% to 5% (37).

In addition, nowadays vit. D is being implemented as a suggested therapy for children and adolescents with depression symptoms. A variety of studies suggest a role of vit. D in the pathogenesis of mental disorders in childhood and adolescence. Findings from supplementation trials seem to support this hypothesis. Randomized controlled trials in childhood and adolescents are urgently needed to support the potential of vit. D as a complementary therapeutic option in mental disorders (38).

Water-soluble vitamins also appear to come into existence with mental health in children and adolescents. According to the results of a 17-years follow-up cross-sectional analysis of the West Australian Pregnancy Cohort study, a lower intake of vitamins B1, B2, B3, B5, B6, and folate was associated with higher externalizing behavior and reduced intake of vitamin B6 and folate was associated with higher internalizing behavior. The study used a collection of a food frequency questionnaire allowing calculation of B-vit. intake. Mental health was assessed using the Youth Self Report which measures total, internalizing (depressed), and externalizing (aggressive) behavior scores. Nevertheless, the role of B complex requires further investigation in randomized controlled trials (39).

Vit. C is a familiar antioxidant involved in stress, anxiety, depression, fatigue, and mood states. Studies claimed that oxidative stress can trigger neuropsychological disorders and antioxidants may play an important resistant key in combating the damage caused by oxidative stress among individuals suffering from anxiety. Accordingly, a hypothesis has arisen suggesting oral supplements of vit. C would reduce anxiety. One study examined the effects of oral vit. C supplementation among 42 high school students (randomized double-blind placebo-controlled trial). The students were given either vit. C 500 mg/day or placebo. The plasma concentrations of vit. C and blood pressure were measured before the intervention and then one day after the intervention. Anxiety levels were investigated for each student before and after 14 days following supplementation. Results showed that vit. C reduced anxiety levels and led to higher plasma vit. C concentration compared to the placebo. The mean heart rates were also significantly different between vit. C group and placebo control group. These study results not only provided evidence that vit. C plays an important therapeutic role for anxiety but also points a possible use of antioxidants in the prevention or reduction of anxiety. This may suggest that a diet rich in vit. C may be an effective adjunct to medical and psychological treatment of anxiety and improve academic performance (40).

Minerals

Minerals are essential nutrients that play a leading role in children's growth and cognition and are essential nutrients to maintain human health. Moreover, minerals take place in multiple processes of metabolism, enzyme systems, electrolyte balance in the body, tissue construction, and cell regeneration. Minerals are found to be of great significance in the rapid growth of children in particular, therefore, detecting the levels of minerals in children may provide better nutrition and health guidance regarding treatment (41).

Minerals are important cofactors for neurotransmission, and as was explained previously, proper neurotransmission is required for the regulation of mood and mental health. Iron is considered important for synaptic function, as iron deficiency has been shown in a large set of preclinical studies to induce changes in electrophysiological properties of neural circuitry and neurotransmitter systems. Iron deficiency manifestation in early life may produce irreversible neural changes when neurogenesis and differentiation of brain regions occur. Several observational studies have shown associations between iron deficiency and poor motor-cognitive development outcomes in children. Some findings from other studies indicate that anemic infants have poorer cognitive capacities, impaired school achievement, and an increase in behavioral difficulties into middle childhood (42). Moreover, iron deficiency is found in children with ADHD and iron concentrations in the umbilical artery are critical during the development of the fetus correlated with children's IQ (4,42). Some additional studies claim that Iron deficiency is also associated with cognitive alterations in adolescents and leads to increased anxiety and/or depression in children with social and attentional problems (43).

Magnesium has an active role in the transport across cell membranes of calcium and potassium. Therefore, in the nervous system, magnesium is significant for neuromuscular coordination and nerve transmission. Furthermore, low magnesium levels may increase glutamatergic neurotransmission, which can lead to oxidative stress and neuronal cell death, and as an outcome precipitate anxiety and depression**.** Magnesium-based supplementation studies have recently concluded that magnesium can be useful in managing mild anxiety symptoms.

Zinc is also related to neurotransmission regulation, high zinc concentrations appear in the synaptic vesicles of specific neurons, playing a role in controlling synaptic excitability. Similar to Mg, zinc protects the brain cells against the potential damage caused by free radicals. (4,42). Another study investigated males 3-20 years of age with a history of assaultive behavior compared with control subjects who did not have such a history. Significant differences in the levels and ratios of serum copper and plasma zinc were found. Frequencies ranged from monthly to many times per day (23).

In recent years, mineral and vitamin depletions are found to be familiar with ASD. The research took a place among 274 children in Hainan china detected that levels of calcium, magnesium, iron and zinc in children with ASD were significantly lower than age-matched typically developing children. This study concluded that children with autism had more vitamin and mineral insufficiencies and their levels were related to ASD symptoms (44).

Water

Water is vital for life and represents a critical nutrient whose absence will be lethal within days. Water comprises from 75% of body weight in infants to 55% in the elderly and is essential for cellular homeostasis, metabolism, substrate transport across membranes, temperature regulation, and circulatory function. Arginine vasopressin or ADH (antidiuretic hormone) is the body's primary water-regulating hormone. It functions to maintain body water balance by allowing the kidneys to alter water excretion in response to the body's needs. Dehydration of a large enough volume is a stimulus for the release of ADH (45,46).

Water deficit produces an increase in the ionic concentration of the extracellular compartment, pulling water from the intracellular compartment and causing cells to shrink. This shrinkage is activating the release of ADH to the kidneys for producing a smaller volume of more concentrated urine. When the body contains an excess of water, the reversing process occurs: the lower ionic concentration of body fluids allows more water to reach the intracellular compartment. The cells are hydrated, drinking is inhibited and the kidneys excrete more water. Water is consumed not only as a beverage but from food and this proportion of water that comes from beverages and food varies with the proportion of fruits and vegetables in the diet (45,46).

Fig.3. Range of water content for selected foods

Percentage	Food Item
100%	Water
90–99%	Fat-free milk, cantaloupe, strawberries, watermelon, lettuce, cabbage, celery, spinach, pickles, squash (cooked)
80–89%	Fruit juice, yogurt, apples, grapes, oranges, carrots, broccoli (cooked), pears, pineapple
70–79%	Bananas, avocados, cottage cheese, ricotta cheese, potato (baked), corn (cooked), shrimp
60–69%	Pasta, legumes, salmon, ice cream, chicken breast
50–59%	Ground beef, hot dogs, feta cheese, tenderloin steak (cooked)
40–49%	Pizza
30–39%	Cheddar cheese, bagels, bread
20–29%	Pepperoni sausage, cake, biscuits
10–19%	Butter, margarine, raisins
1–9%	Walnuts, peanuts (dry roasted), chocolate chip cookies, crackers, cereals, pretzels, taco shells, peanut butter
0%	Oils, sugars

Figure 3 the ranges of water in various foods Source: The USDA National Nutrient Database for Standard Reference, Release 21 provided in Altman (45).

The recommended daily water intake depends on age, sex, weight, activity status, air temperature, and humidity. For infants weighing between 3.5-10 kg, the daily fluid requirement is 100 ml/kg. For children 11-20 kg, the daily water requirement is 100 ml/kg for the first 10 kg and 50 ml/kg for every kg above 10 kg. For children above 20 kg, the fluid requirement is calculated as 1500ml for 20 kg and 20 ml/kg for every kg above 20 kg. However, more than 2400ml of fluid should not be administered at once (47).

Nowadays, hydration seems closer to exposing productivity in improving mental states. Water intake has beneficial effects in low water volume consumers, especially sleep-wake feelings, whereas decreasing water intake has damaging effects on mood in high water volume consumers. These effects were shown to impact calmness, satisfaction, and positive emotions (48).

In the recent decade, a prevalent hypothesis has arisen claiming that changes in hydration status throughout the day may affect cognitive performance with implications for learning success in the classroom for children. This theory is now more based thanks to the studies and investigations that shed some light on this issue. These data showed that not only performance but also mood tend to be impaired by dehydration in children. Well-hydrated children tended to perform better than dehydrated children also by the aspect of working memory measures.

Accordingly, researchers concluded that dehydration was a common phenomenon in schoolchildren and that this may impair their cognitive functioning. Moreover, one of the studies showed that habitual water intake was significantly correlated with high-level cognitive control abilities. Low drinkers had worse reaction times and committed more inhibition errors during the most demanding condition, thus providing water to schoolchildren during class hours has a beneficial effect following these studies (49).

Conclusions

Nutrition can influence mental health disorders and status and may help in controlling symptoms. Low carbohydrate consumption in diet may tend to precipitate depression since the production of serotonin is triggered by carbohydrates, however high consumption may worsen symptoms of Attention deficit hyperactivity disorder, externalizing behaviors, and sleeping problems in children.

Amino acids can precipitate mood changes and worsening symptoms of mental health conditions. Omega-3 essential fatty acids were shown to be related to mood changes, depression, and attention deficit hyperactivity disorder, this may be explained due to omega-3 inhibitory action of inflammatory cytokines that are associated with inducing depression and low mood together with decreasing neurotransmitters availability.

Supplementation of vitamins shows some rigid proof of successful intervention among children with a variety of mental health conditions. Children with autism spectrum disorder exhibited a significant improvement of symptoms with vitamin A supplementations. Vitamin D may have the potential as a complementary therapeutic option for depression and other mental health disorders. Vitamin D improves core symptoms of autistic children with supplementation during pregnancy, infancy, and early childhood.

Low or high intake of vitamin B complex group may have a strong association with the control of internalizing and externalizing behavior in children. Vitamin C can reduce anxiety.

Poorer cognitive capacity and impaired school achievement are associated with iron deficient anemia. Magnesium may be clinically used for mild anxiety symptoms. Adequate water intake is correlated with high-level cognitive control abilities.

References

1) Adrienne O'Neil, Shae E. Quirk, Siobhan Housden, Sharon L. Brennan, Lana J. Williams, Julie A. Pasco "et al." Relationship Between Diet and Mental Health in Children and Adolescents: A Systematic Review [Internet]. Published online; October 2014. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4167107/
2) Yong-Ku Kim, Cheolmin Shin*. The Microbiota-Gut-Brain Axis in Neuropsychiatric Disorders: Patho-physiological Mechanisms and Novel Treatments [Internet]. Published online; Jun 2018. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5997867/
3) Marilia Carabotti, Annunziata Scirocco, Maria Antonietta Maselli, and Carola Severia. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems [internet]. 2015 Apr-Jun. Available from: The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems (nih.gov)
4) T. S. Sathyanarayana Rao, M. R. Asha, B. N. Ramesh, and K. S. Jagannatha Rao. Understanding nutrition, depression and mental illnesses [Internet]. Published online; 2008 Apr-Jun. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2738337/
5) Holesh JE, Aslam S, Martin A. Physiology, Carbohydrates. [Updated 2021 Jul 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459280/#!po=82.1429
6) Barbara E. Goodman. Insights into digestion and absorption of major nutrients in humans [internet]. Division of Basic Biomedical Sciences, Sanford School of Medicine, University of South Dakota, Vermillion, South Dakota. Submitted 22 October 2009; accepted in final form 5 February 2010. Available from: https://journals.physiology.org/doi/epdf/10.1152/advan.00094.2009
7) Zhuo Fu, Elizabeth R. Gilbert, and Dongmin Liu. Regulation of Insulin Synthesis and Secretion and Pancreatic Beta-Cell Dysfunction in Diabetes [internet]. Curr Diabetes Rev. 2013 Jan. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3934755/
8) Dawn M Richard, Michael A Dawes, [...], and Donald M Dougherty. L-Tryptophan: Basic Metabolic Functions, Behavioral Research and Therapeutic Indications [internet].

Published online; 2009 Mar 23. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2908021/#!po=2.69461

9) Gabriela Precup, Dan-Cristian Vodnar. Gut Prevotella as a possible biomarker of diet and its eubiotic versus dysbiotic roles: a comprehensive literature review [internet]. British journal of nutrition; 2019 Jul 28. Available from: https://pubmed.ncbi.nlm.nih.gov/30924428/

10) Amy Loughmana, Anne Louise Ponsonby ,Martin O'Hely, Christos Symeonides, Fiona Collier, Mimi L.K.Tang “et al.” Gut microbiota composition during infancy and subsequent behavioural outcomes [internet]. Published online; 12 February 2020. Available from: https://www.sciencedirect.com/science/article/pii/S2352396420300153

11) Weronika Wasyluk , gabriela zdunek , agnieszka pedrycz. The impact of carbohydrate intake on the behavior and cognitive functions of children and adolescents [internet]. Pol J Public Health 2019;129(2): 64-67. Available from: file:///C:/Users/user/Downloads/The_impact_of_carbohydrate_intake_on_the_behavior_%20(1).pdf

12) Sarah Lee Blunden, Catherine M Milte, Natalie Sinn. Diet and sleep in children with attention deficit hyperactivity disorder: preliminary data in Australian children [internet]. University of South Australia, Adelaide, South Australia. J Child Health Care. 2011;15(1):14-24. Available from: https://pubmed.ncbi.nlm.nih.gov/21317167/

13) Leila Azadbakht, Ahmad Esmaillzadeh. Dietary patterns and attention deficit hyperactivity disorder among Iranian children [internet]. Nutrition. 2012 Mar;28(3):242-9. Available from: https://pubmed.ncbi.nlm.nih.gov/21868196/

14) Jansen, E.C., Miller, A.L., Lumeng, J.C. et al. Externalizing behavior is prospectively associated with intake of added sugar and sodium among low socioeconomic status preschoolers in a sex-specific manner. Int J Behav Nutr Phys Act 14, 135 (2017). Available from: https://doi.org/10.1186/s12966-017-0591-y

15) Lopez MJ, Mohiuddin SS. Biochemistry, Essential Amino Acids. [Updated 2021 Mar 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557845/#_NBK557845_pubdet_

16) Preeti Khanna, Vijay K. Chattu, and Bani T. Aeri. Nutritional Aspects of Depression in Adolescents - A Systematic Review [internet]. Published online 2019 Apr 3. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6484557/#__ffn_sectitle

17) Benjamin E. Jewett; Sandeep Sharma. Physiology, GABA. [Updated 2021 Jul 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513311/#!po=79.1667

18) Mary J. Allen; Sarah Sabir; Sandeep Sharma. GABA Receptor. [Updated 2021 Feb 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526124/#_NBK526124_pubdet_

19) Richard A. E. Edden, PhD, Deana Crocetti, PhD, He Zhu, PhD, Donald L. Gilbert, MD, and Stewart H. Mostofsky, MD. Reduced GABA Concentration in Attention-Deficit/Hyperactivity Disorder [internet]. Arch Gen Psychiatry. Author manuscript; available in PMC 2014 Mar 31. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3970207/

20) Evert Boonstra, Roy de Kleijn, Lorenza S. Colzato, Anneke Alkemade, Birte U. Forstmann, and Sander Nieuwenhuis. Neurotransmitters as food supplements: the effects of GABA on brain and behaviour [internet]. Front Psychol. 2015; 6: 1520. Published online 2015 Oct 6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4594160/

21) Matteo Briguglio, Bernardo Dell'Osso, Giancarlo Panzica, Antonio Malgaroli, Giuseppe Banfi, Carlotta Zanaboni Dina, Pasco "et al." Dietary Neurotransmitters: A Narrative Review on Current Knowledge [internet]. Published online 2018 May 10. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5986471/

22) Smriga M, Ghosh S, Mouneimne Y, Pellett PL, Scrimshaw NS. Lysine fortification reduces anxiety and lessens stress in family members in economically weak communities in Northwest Syria. Proc Natl Acad Sci U S A. 2004 Jun 2004 May 24. Available from: https://pubmed.ncbi.nlm.nih.gov/15159538/

23) Ruth Leyse-Wallace. Nutrition and mental health. [International Standard Book Number-13: 978-1-4398-6336-7 (eBook - PDF)]. Taylor & Francis Group 6000 Broken Sound

Parkway NW, Suite 300 Boca Raton, FL 33487-2742. © 2013 by Taylor & Francis Group, LLC.

24) Sam C, Bordoni B. Physiology, Acetylcholine. [Updated 2021 Apr 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557825/#_NBK557825_pubdet_

25) Joanna C. Hamlin, Margaret Pauly, Stepan Melnyk, Oleksandra Pavliv, William Starrett, Tina A. Crook, S. Jill James, "Dietary Intake and Plasma Levels of Choline and Betaine in Children with Autism Spectrum Disorders", Autism Research and Treatment, vol. 2013, Article ID 578429, 7 pages, 2013. https://doi.org/10.1155/2013/578429

26) Eoin Fahy, Dawn Cotter, Manish Sud, and Shankar Subramaniam. Lipid classification, structures and tools [internet]. Biochim Biophys Acta. 2011 Nov; 1811(11): 637–647. Published online 2011 Jun 16. Available from: Lipid classification, structures and tools - PMC (nih.gov)

27) Saba Ahmed; Parini Shah; Owais Ahmed. Biochemistry, Lipids [internet]. [Updated 2021 May 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: Biochemistry, Lipids - StatPearls - NCBI Bookshelf (nih.gov)

28) Laura Bordoni, Irene Petracci, Fanrui Zhao, Weihong Min, Elisa Pierella, Taís Silveira Assmann, "et al." Nutrigenomics of Dietary Lipids [internet]. Antioxidants (Basel). 2021 Jun 22. Available from: Nutrigenomics of Dietary Lipids - PMC (nih.gov)

29) Mauro G Di Pasquale. The essentials of essential fatty acids [internet]. J Diet Suppl. 2009;6(2):143-61. Available from: The essentials of essential fatty acids - PubMed (nih.gov)

30) Pawels EK, Volterrani D. Fatty acid facts, Part I. Essential fatty acids as treatment for depression, or food for mood? Drug News Perspect. 2008 Oct;21(8):446-51. Available from: Fatty acid facts, Part I. Essential fatty acids as treatment for depression, or food for mood? - PubMed (nih.gov)

31) Derbyshire E. Do Omega-3/6 Fatty Acids Have a Therapeutic Role in Children and Young People with ADHD? [internet]. J Lipids. Published online 2017 Aug 30. Available from: Do Omega-3/6 Fatty Acids Have a Therapeutic Role in Children and Young People with ADHD? - PMC (nih.gov)

32) Barbora Katrenčíková, Magdaléna Vaváková, Iveta Waczulíková, Stanislav Oravec, Iveta Garaiova, Zuzana Nagyová "et al." Lipid Profile, Lipoprotein Subfractions, and Fluidity of Membranes in Children and Adolescents with Depressive Disorder: Effect of Omega-3 Fatty Acids in a Double-Blind Randomized Controlled Study [internet]. Biomolecules. Published online 2020 Oct 8. Available from: Lipid Profile, Lipoprotein Subfractions, and Fluidity of Membranes in Children and Adolescents with Depressive Disorder: Effect of Omega-3 Fatty Acids in a Double-Blind Randomized Controlled Study - PMC (nih.gov)
33) Isabelle Häberling, Gregor Berger, Klaus Schmeck, Ulrike Held, and Susanne Walitza, The Omega-3 Study Team. Omega-3 Fatty Acids as a Treatment for Pediatric Depression. A Phase III, 36 Weeks, Multi-Center, Double-Blind, Placebo-Controlled Randomized Superiority Study [internet]. Front Psychiatry. Published online 2019 Nov 27. Available from: Omega-3 Fatty Acids as a Treatment for Pediatric Depression. A Phase III, 36 Weeks, Multi-Center, Double-Blind, Placebo-Controlled Randomized Superiority Study - PMC (nih.gov)
34) Reddy P, Jialal I. Biochemistry, Fat Soluble Vitamins. [Updated 2021 Sep 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: Biochemistry, Fat Soluble Vitamins - StatPearls - NCBI Bookshelf (nih.gov)
35) Lykstad J, Sharma S. Biochemistry, Water Soluble Vitamins. [Updated 2021 Mar 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: Biochemistry, Water Soluble Vitamins - StatPearls - NCBI Bookshelf (nih.gov)
36) Min Guo, Jiang Zhu , Ting Yang , Xi Lai, Xiao Liu, Juan Liu "et al." Vitamin A improves the symptoms of autism spectrum disorders and decreases 5-hydroxytryptamine (5-HT): A pilot study[internet]. Brain Res Bull. 2018 Mar. Available from: Vitamin A improves the symptoms of autism spectrum disorders and decreases 5-hydroxytryptamine (5-HT): A pilot study - PubMed (nih.gov)
37) John Jacob Cannell. Vitamin D and autism, what's new? [internet]. Rev Endocr Metab Disord 18, 183–193 (2017). Available from: Vitamin D and autism, what's new? | SpringerLink

38) Manuel Föcker, Jochen Antel, Stefanie Ring, Denise Hahn, Özlem Kanal, Dana Öztürket al. Vitamin D and mental health in children and adolescents [internet]. Eur Child Adolesc Psychiatry 26, 1043–1066 (2017). https://doi.org/10.1007/s00787-017-0949-3

39) Carly E. Herbison, Siobhan Hickling, Karina L.Allen, Therese A. O'Sullivan Monique Robinson, Alexandra P. Bremner "et al." Low intake of B-vitamins is associated with poor adolescent mental health and behaviour [internet]. Available online 23 September 2012. Available from: Low intake of B-vitamins is associated with poor adolescent mental health and behaviour - ScienceDirect

40) Ivaldo Jesus Lima de Oliveira, Victor Vasconcelos de Souza, Vitor Motta, Sérgio Leme Da-Silva. de Oliveira IJ, de Souza VV, Motta V, Da-Silva SL. Effects of Oral Vitamin C Supplementation on Anxiety in Students: A Double-Blind, Randomized, Placebo-Controlled Trial [internet]. Pak J Biol Sci. 2015 Jan. Available from: Effects of Oral Vitamin C Supplementation on Anxiety in Students: A Double-Blind, Randomized, Placebo-Controlled Trial - PubMed (nih.gov)

41) Xiaofeng Li, Chunnan Wang, Yang Wang, Xusheng Zhao & Na Li. Determination of 11 minerals in children using inductively coupled plasma mass spectrometry [internet]. BMC Pediatr 21, 483 (2021). Available from: https://doi.org/10.1186/s12887-021-02962-z

42) Anne-Laure Tardy, Etienne Pouteau, Daniel Marquez, Cansu Yilmaz, and Andrew Scholey. Vitamins and Minerals for Energy, Fatigue and Cognition: A Narrative Review of the Biochemical and Clinical Evidence [internet]. Published online 2020 Jan 16. Available from: Vitamins and Minerals for Energy, Fatigue and Cognition: A Narrative Review of the Biochemical and Clinical Evidence - PMC (nih.gov)

43) Jonghan Kim1 and Marianne Wessling-Resnick. Iron and mechanisms of emotional behavior. The Journal of nutritional biochemistry [internet]. 25(11), 1101–1107. Available from: https://doi.org/10.1016/j.jnutbio.2014.07.003

44) Min Guo, Ling Li, Qian Zhang, Li Chen, Ying Dai, Liyan Liu "et al." Vitamin and mineral status of children with autism spectrum disorder in Hainan Province of China: associations with symptoms [internet]. Nutr Neurosci. 2020 Oct;23. Available from: Vitamin and mineral status of children with autism spectrum disorder in Hainan Province of China: associations with symptoms - PubMed (nih.gov)

45) Lawrence E. Armstrong and Evan C. Johnson. Water Intake, Water Balance, and the Elusive Daily Water Requirement [internet]. Nutrients. 2018 Dec published online. Available from: Water Intake, Water Balance, and the Elusive Daily Water Requirement - PMC (nih.gov)
46) Barry M. Popkin, Kristen E. D'Anci, and Irwin H. Rosenberg. Water, hydration, and health. Nutr Rev. 2010 [internet]. Available from: Water, hydration, and health | Nutrition Reviews | Oxford Academic (oup.com)
47) Unaiza Faizan, Audra S. Rouster. Nutrition and Hydration Requirements In Children and Adults. [Updated 2021 Sep 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: Nutrition and Hydration Requirements In Children and Adults - StatPearls - NCBI Bookshelf (nih.gov)
48) Nathalie Pross, Agnès Demazières, Nicolas Girard, Romain Barnouin, Déborah Metzger, Alexis Klein, "et all". Effects of Changes in Water Intake on Mood of High and Low Drinkers [internet]. PLoS One. 2014 April. Available from: Effects of Changes in Water Intake on Mood of High and Low Drinkers - PMC (nih.gov)
49) Nathalie Pross. Effects of Dehydration on Brain Functioning: A Life-Span Perspective [internet]. Epub 2017 Jun 15. Available from: Effects of Dehydration on Brain Functioning: A Life-Span Perspective - FullText - Annals of Nutrition and Metabolism 2017, Vol. 70, Suppl. 1 - Karger Publishers