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Animals and Environment

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Impact of nutrition on mental health and the role of different dietary approaches to improve depression and mood disorders: a systematic review

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Abstract

In the last years, scientifical research has showed increased interest in the individual well-being. Evidence is growing, that diet plays an important role in psychological and physical well-being. Depression is a prevalent mental disorder that adversely affects various aspects of life, including personal, communal, professional, and educational domains. Globally 3.8% of the population is affected, regardless of the background.

Depression arises from an interplay of social, psychological, and biological factors: age, gender, environmental influences. Risk factors are negative life events, trauma, stress, along with a personal or family history of depression. Depression often coexists with other medical conditions. In depressive disorders are involved biological mechanisms including deficiencies in norepinephrine, serotonin, and dopamine; alterations of the hypothalamic-pituitary-adrenal axis; low levels of brain-derived neurotrophic factor (BDNF). Inflammation and immune system alterations are also involved. Gut-microbiota-brain axis plays a role in depression. Diet can affect gut microbiota: a healthy diet improves microbiota and cognitive function, while Western diet can cause dysbiosis and inflammation.

Other factors that are involved in the development of depressive disorder are circadian rhythms, regulated by light and external stimuli, which are crucial for metabolism and mood. Disruptions from irregular meals and poor diets are linked to obesity and depression. Physical activity is vital for preventing and treating depression.

Focusing on diet could be a strategy to improve depressive symptoms. In this thesis we analyze two different dietary approaches: vegan/vegetarian diets and the Mediterranean diet.

The aim of this work is to systematically review data on the correlation between diet and depression. The research seeks to assess how these dietary approaches impact on psychological well-being, quality of life, and symptoms of depression. The systematic research was carried out using Pubmed database. Two separate systematic reviews were conducted: one for vegetarian/vegan diets and one for Mediterranean diet and their effect on depression, quality of life, and weight.

Riassunto

Negli ultimi anni la ricerca scientifica ha dimostrato crescente interesse nel benessere dell'individuo. È sempre più evidente come l'alimentazione giochi un ruolo importante nel benessere fisico ma anche mentale. La depressione è un disturbo mentale diffuso, che influisce negativamente su vari aspetti della vita, inclusi quelli personali, comunitari, professionali e educativi. Il 3.8% della popolazione globale ne è colpito, indipendentemente dalla provenienza.

La depressione insorge dall'interazione di fattori sociali, psicologici e biologici: età, genere, influenze ambientali. Tra i fattori di rischio troviamo: eventi negativi, traumi, stress, storia familiare o personale di depressione. La depressione spesso coesiste con altre condizioni mediche. Nel disturbo depressivo sono coinvolti meccanismi biologici, tra cui carenze di noradrenalina, serotonina e dopamina; alterazioni dell'asse ipotalamo-ipofisi-surrene; bassi livelli di fattore neurotrofico cerebrale. Sono coinvolte anche alterazioni del sistema immunitario e infiammazione. Anche l'asse intestino-microbiota-cervello gioca un ruolo nella depressione. La dieta può influenzare il microbiota intestinale: una dieta sana migliora il microbiota e la funzione cognitiva, mentre una dieta standard americana può causare disbiosi e infiammazione.

Altri fattori che giocano un ruolo nello sviluppo del disturbo depressivo sono i ritmi circadiani, regolati dalla luce e dagli stimoli esterni, che sono fondamentali per il metabolismo e l'umore. Le perturbazioni dovute a pasti irregolari e diete povere sono legate all'obesità e alla depressione. L'attività fisica è fondamentale per la prevenzione e il trattamento della depressione.

Concentrarsi sulla dieta potrebbe essere una strategia per migliorare i sintomi depressivi. In questa tesi andremo ad analizzare due approcci dietetici differenti e i loro effetti sulla depressione: la dieta vegetariana/vegana e la dieta mediterranea.

Lo scopo di questo lavoro è raccogliere sistematicamente i dati sulla correlazione tra dieta e depressione. La ricerca mira a valutare come questi approcci dietetici influenzino il benessere psicologico, la qualità della vita e i sintomi della depressione. La ricerca sistematica è stata condotta utilizzando il database Pubmed. Sono state effettuate due review sistematiche separate: una per le diete vegetariane/vegane e una per la dieta mediterranea e il loro effetto sulla depressione, la qualità della vita e il peso.

1. Introduction

1.1 Depression

Depression is a common mental disorder which negatively affects life in all its aspects. Depression can impact not only at individual level but also in the community and at home, work, and school. Depression has an impact of the 3.8% in the global population, and it can happen to anyone. Depression results from multifactorial causes: social, psychological, and biological factors like genetics, age, gender, and the environment (WHO, 2023).

As indicated in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, depressive disorders are characterized by sadness severe enough or persistent enough to interfere with function and often by decreased interest or pleasure in activities. To be diagnosed with depression, other symptoms should be present: sleep disturbances, poor concentration or indecisiveness, fatigue, decreased or increased appetite, psychomotor agitation or retardation, feelings or worthlessness or excessive or inappropriate guilt, suicidal thoughts (DSM-5, 2013).

Risk factors of depression are not only negative life events like trauma or stress, but also personal or family history of depression. Depression can present comorbidity with other medical illnesses. In this case, often people with both depression and medical illness have more severe symptoms of both (NIHM, 2024).

The biological mechanisms behind the major depression disorder are several. The noradrenergic and serotonergic systems constitute a complex system capable of modulating areas of feeling, thinking, and behaving. Deficiencies in norepinephrine and serotonin have been associated with depression. Tryptophan is a limiting amino acid for serotonin synthesis in the brain. It was seen that tryptophan depletion does not cause depression in healthy people, but it induces a relapse in patients recovering from depression. This demonstrates that norepinephrine and serotonin deficiencies play a role in depression, but other neurochemical factors are needed to induce depression.

The hypothalamic-pituitary-adrenal axis can be altered in depression, and its mechanism can be seen in Figure 1. In response to stress, the hypothalamus releases the corticotropin-releasing hormone (CRH) into the pituitary receptors. Following this stimulus, corticotropin is released in the plasma, stimulating corticotropin receptors in the adrenal cortex, resulting in release of cortisol in the blood. The response of the hypothalamic cortisol receptors is the decrease of CRH production to maintain homeostasis. Cortisol and CRH are involved in depression: elevated cortisol plasma levels and elevated CRH levels in cerebrospinal fluid are found in patients with

depression. It is also possible a pathogenic role in depression is represented by the chronic mild increased levels of cortisol, especially at night when levels are normally very low.

Brain-derived neurotrophic factor (BDNF) is a neurotrophic peptide, critical for axonal growth, neuronal survival, and synaptic plasticity. BDNF levels are affected by stress and cortisol. In patients with depression, BDNF levels decrease in the hippocampus. Hippocampal size and numbers of neurons and glia are decreased, probably reflecting reduced neurogenesis due to elevated cortisol levels and reduced BDNF (Belmaker and Agam, 2008).

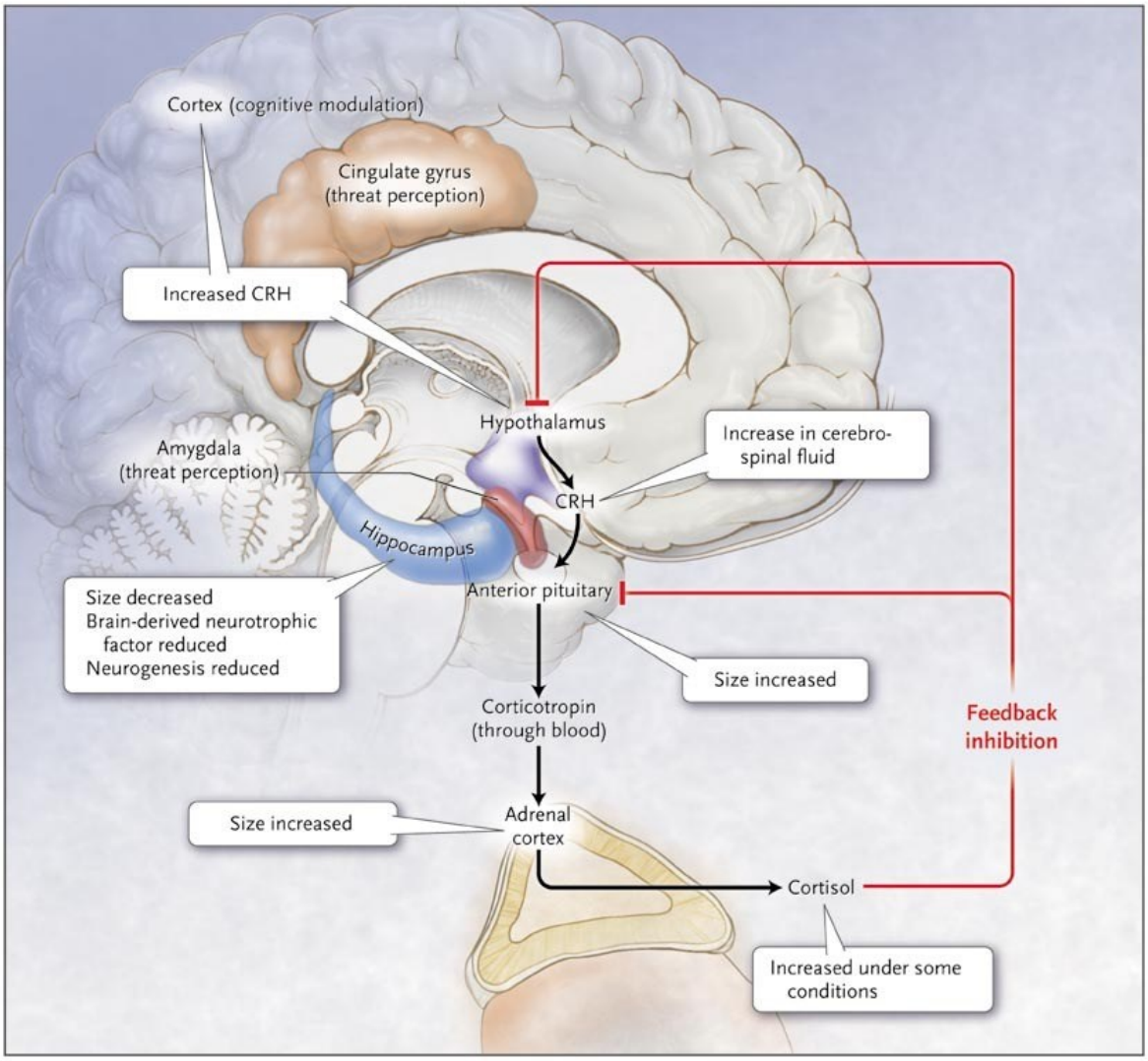


Figure 1. The Hypothalamic-Pituitary-Cortisol system in depression (Belmaker and Agam, 2008)

The immune system is involved in the pathogenesis of depression: increased peripheral pro-inflammatory cytokines production, dysregulation of T-cell function, and altered neuroinflammatory signaling are present in depression. Clinical evidence showed a relation

between low-grade inflammation and abnormal activity of inflammatory mediators in patients affected by depression.

In the brain is present a neuroimmune machinery, which includes astrocytes, oligodendrocytes, and microglia. Microglia secrete pro-inflammatory mediators after infection or brain damage, which are linked to neurodegenerative and psychiatric disorders including major depressive disorder. Abnormal activation of microglia in prefrontal cortex and anterior cingulate cortex was found during severe episodes of depression.

Evidence showed that pathophysiology of depression also includes the immune system and the gut microbiota. Most of the antidepressants used in clinical practice are represented by drugs that target serotonin and noradrenaline pathways. Where antidepressant alone are not effective, adjunctive therapies can increase the efficacy. Exercise and diet modification have anti-inflammatory effects and modulate the gut-brain-associated pathways to reduce effects of depression (Donoso et al., 2022).

The pathophysiology of depression is yet not completely defined, but diet may be considered a modifiable risk for depression, depending on the type of eaten foods (O'Neil et al., 2022). In our modern society depression can be associated with nutritional problems: excessive energy intake and "Westernization" of the diet, which is characterized by lower content of micronutrients and polyphenols and ultra-processed foods. Excessive energy intake is strongly related to weight gain and obesity, diabetes, and metabolic syndrome. Treating these conditions can be a help both for physical and mental health, improving depressive symptoms and associated cognitive impairment. For this reason, caloric restriction may have an antidepressant effect (Kunugi, 2023). Hypocaloric diets have beneficial effects since they cause weight loss, which is known to be positive for depression. The reason behind this improvement can be found also in a better social life, because often overweight represents a stigma (Paris et al., 2024).

1.2 Gut microbiota-brain axis and depression

The gut microbiota is the microbial community that occupies the gastrointestinal tract, with distinct physio-chemical properties. The microbiota-gut-brain axis is the bidirectional communication between the central nervous system and all the microorganisms living in the gastrointestinal tract. Depression has been associated with alterations in gut microbiota (Donoso et al., 2022).

Neuronal, endocrine, and immunoregulatory pathways assist the communication between the gut microbiota and the brain. The Central Nervous System (CNS) can directly modulate the function

and composition of the gut microbiota through the autonomic nervous system. Indirect pathways help in this modulation, such as:

1) Luminal release of neurotransmitters
2) Permeability of the intestinal barrier and secretion of mucus
3) Regional regulation of gastrointestinal transit and motility (Ross et al., 2024).

Microbiota alterations modulate signaling systems, of which the most important pathways are:

- γ-Aminobutyric acid (GABA) dysfunction in signaling is connected to anxiety and depression. In culture Lactobacillus and Bifidobacterium can metabolize glutamate to produce GABA. Also evidences *in vivo* mice were found.
- Serotonergic system underlies in the pathogenesis of mood disorders and in the neurobiology of anxiety. Studies showed a correspondence between microbiota and serotonin (Foster and Neufeld, 2013).

The signaling pathway of the essential amino acid tryptophan is fundamental to produce serotonin and other molecules involved in neuroendocrine signaling and pathology. Serotonin has an important role in the development of psychiatric disorders. Gut microbiota can modulate tryptophan into various metabolites like kynurenine, tryptamine, and indoles. These metabolites modulate the CNS via bloodstream or by activating vagal afferents, consequently they are important in neuroendocrine and neuroimmune processes. Microbe-dependent metabolites have an important role in modulating functions of both peripheral and central nervous systems, but it is yet to be established if they have a causal role in developing human psychiatric diseases (Ross et al., 2024).

Animal models utilize germ-free (GF) mice, that are born in aseptic conditions. Brain and gut biochemistry were different in GF animals and control animals with normal or pathogen-free flora. Studies showed that infection with pathogens increased emotional behavior. Results in animals with normal flora after administration of probiotics showed reduced depression-like behaviors, which were been induced by maternal separation and experimental myocardial infarction. Different studies in rodents showed a role of the gut microbiota in modulating emotional, nociceptive, and feeding behavior in rodents. Since humans cannot be studied germ-free, it is important to be careful when extrapolating these data to humans. Other encountered difficulties in human studies are the complexity of the human gut microbiota which can be affected by diet, sex-related differences, and genetic variations, and the challenge of measuring changes in human emotions and cognitive functions (Mayer et al., 2015).

Gut microbiota is both causal of depression and altered by depression: alteration in the gut microbiota influences emotions, while changes in the brain can alter the composition and function of gut microbiota. Phyla that were found changed with depression are decreased *Firmicutes*, and increased *Bacteroidetes* and *Proteobacteria*. Since modification in gut microbiota can lead to depression, use of antibiotics, that are known to cause damage to the microbiota can increase patient susceptibility to depression (Kim et al., 2023).

In animal models, transplantation of the gut microbiota from individual with depression into germ-free mice and rats showed increased depressive-like behaviors, suggesting that with the microbiota were also transferred the phenotypes of depression. Changes in host physiology were the activation of the hypothalamic-pituitary-adrenal (HPA) axis and increases in inflammation in the brain.

The HPA axis regulates the production of glucocorticoids and the regulation of BDNF. Glucocorticoids are important in inducing anti-inflammatory responses in stress conditions. The dynamic regulation of the body in response to stress is called allostasis and involves also the HPA axis. In depression the mechanism of allostasis often fails. In mouse models was found that the gut microbiota helps the allostasis and it can be restored with the administration of *Lactobacillus* spp. normalizing levels of glucocorticoids (Morais et al., 2021).

Since microbiota restoration can improve depressive symptoms, probiotics and fecal microorganisms' transplantation can be used as alternative or adjunctive antidepressive treatment. It was found that also healthy diets and prebiotics can have benefits, not only in the gut but also in the gut-brain axis (Kim et al., 2023).

A potential consequence of the alteration of gut microbiota composition and diversity in patients with depression is an increase in neuroinflammation. In germ-free mice were seen substantial differences in microglial density and morphology. Findings suggest that gut microbiome plays a role in the regulation of microglial maturation and function. Microglial homeostasis can be disrupted in depression, for this reason a possibility is that microbiota-gut-brain axis is involved in immune-related depression. Further studies are needed to understand if the gut microbiota may contribute to the development and onset of depressive symptoms (Donoso et al., 2022).

1.3 Nutrition influence on gut microbiota and depression

Healthy diets can improve the presence of beneficial microorganisms and improve cognitive functions and behavior, through the gut-brain axis. Recent studies found benefits for the diet therapy in treating major depression (Kim et al., 2023).

Dietary fiber promotes the growth of beneficial species like *Bifidobacterium* and *Lactobacillus*. Consumption of dietary fiber in patients with depression was lower compared with healthy control. Intake of more fibers was associated with lower probability of depression.

Probiotics can help with depression because they help alleviating the stress-induced depression and its correlated changes in brain. Since patients with depression are found to have lower presence of *Lactobacillus* and *Bifidobacterium*, probiotics can improve the gut microbiota and relieve stress and depression symptoms (Kunugi, 2023).

Diet can influence the gut microbiota regulating the intestinal immune system. It influences the permeability of the epithelial barrier and enables the translocation of microbial membrane components. This can lead to metabolic endotoxemia[1]. Gut microbes can influence the body's immune system by directly activating immune cells in the gut, leading to pro- and anti-inflammatory responses. Preclinical studies showed a link between metabolic endotoxemia, neuroinflammation and impaired brain function in psychiatric disorders (Ross et al., 2024). Metabolic endotoxemia caused by increased gut permeability is associated with the Western diet. This unhealthy dietary pattern can lead to microbial dysbiosis, which can trigger significant grades of inflammation driven by high abundance of proinflammatory microorganisms promoting immune intolerance (Gundogdu and Nalbantoglu, 2023).

Diet-derived microbial metabolites have effects on the brain, which are reported in the Figure 2. Short-chain fatty acids (SCFAs) are microbial metabolites with strong peripheral and central anti-inflammatory properties. Their synthesis is performed by several species of gut microbes that ferment complex carbohydrates, including *Eubacterium rectale*, *Eubacterium hallii*, *Faecalibacterium prausnitzii*, and *Ruminococcus bromii*. Of these SCFAs, butyrate can directly reduce the expression of genes related to inflammatory pathways in the intestinal tissue. Microbe-generated butyrate was shown to have anti-inflammatory effects in the brain.

Dietary changes in the gut microbiota composition can indirectly regulate the microglia in the CNS, affecting their maturation and functioning. Microglia are the predominant immune cells in the brain and for their optimal functioning the presence of beneficial gut bacteria is important. Administration of SCFAs resulted in restored microglia function in case of impairment.

[1] Metabolic endotoxemia was first defined as a diet-induced, 2–3-fold increase in plasma liposaccharide levels associated with low-grade inflammation. It causes a state of low-grade inflammation, which is a pathological feature of a range of chronic conditions including type 2 diabetes mellitus, non-alcoholic fatty liver disease, chronic kidney disease, and atherosclerosis (Mohammad and Thiemermann, 2021).

Microglia disfunction and gut microbial dysbiosis are linked to psychiatric disorders including depression (Ross et al., 2024).

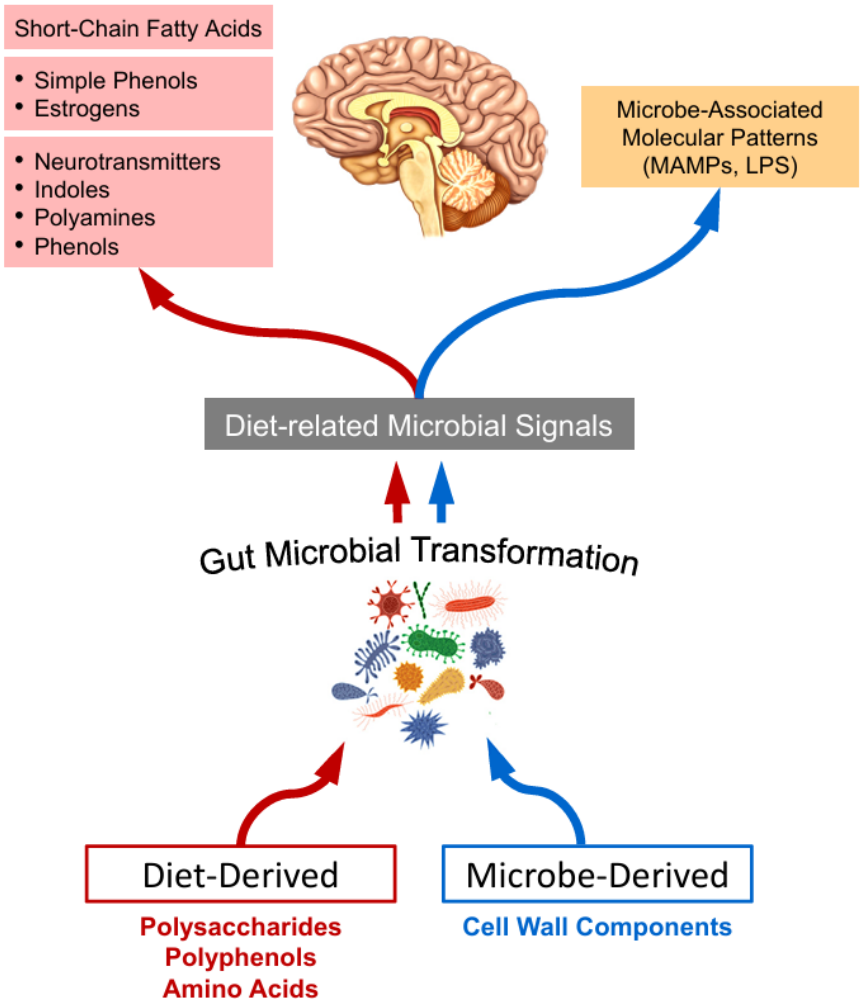


Figure 2. Diet-related and microbial signaling molecules influencing brain function. Molecules interact on brain target to modify brain networks. Diet influences composition and function of the gut microbiota, which in turn metabolize large diet-derived molecules into neuroactive substances. LPS, lipopolysaccharide. MAMP, microbe-associated molecular pattern. Image from Ross et al., 2024.

1.4 Role of nutrients in treating depression

Dietary patterns are defined as 'the quantity, variety, or combination of different foods and beverages in a diet, and the frequency with which they are habitually consumed'. Recent theories determined that dietary patterns may impact mood due to different nutrient profiles and biological mechanisms (Walsh et al., 2023).

Diet and nutrition have an important role in prevention and treatment of depression. Nutrition can significantly influence the onset, the severity, and the course of depression. Impact of nutrition on thinking, acting, and feeling is studied by dietary neuroscience. Since nutritional advice is rarely

given to mental patients, nutritional psychiatry's aim is to apply dietary intervention in the management of mental health problems, for example depression.

Food needs to be balanced to think and act well. Several neurotransmitters are activated to regulate mental faculties and emotions. Nutrients and neurotransmitters interact differently resulting in different moods (Sharma et al., 2023).

Low tryptophan in the diet was found to increase depression symptomology (O'Neil et al., 2022). Also, other amino acids are normally lower in patients with depression: phenylalanine, tyrosine, and methionine. They are precursors of monoamines like serotonin, dopamine, and noradrenaline which are important for feeling well, leading to the hypothesis that enough protein intake may protect against depression (Kunugi, 2023).

Foods high in polyphenols and flavonoids can reduce depression not only by improving the composition of gut microbiota as previously discussed, but also thanks to their antioxidant and anti-inflammatory functions. Adherence to the Mediterranean diet, which is known to be rich in flavonoids, polyphenols and tryptophan, can help with reducing depression symptoms (O'Neil et al., 2022).

Vitamins:

- Low folate concentration is related with depression. A possible strategy is to measure folate concentration in blood and based on results provide patients with folate supplements.
- Vitamins of the B group are also needed to be checked, to avoid deficiencies which are related to depression (Kunugi, 2023). B vitamins have an important role as cofactor in neurotransmitter production and function so they are needed by the central nervous system to function correctly.
- Vitamin D is needed for processes in the brain like neuroimmunomodulation, neuroplasticity, neuroprotection, and brain development, meaning it can be connected to depressive disorders (Sharma et al., 2023).

  Vitamin D is characterized by seasonal decrease in winter due to less exposure to the sun; it could have a role in seasonal depression. Some early studies report the efficacy of vitamin D supplement for seasonal depression and for mood-enhancing in healthy people in winter (Kunugi, 2023).

Carbohydrates: they affect mood and behavior. After eating carbohydrates, insulin is released and facilitates the passage of blood sugar into cells. Insulin is linked to tryptophan absorption in brain,

and tryptophan help inducing the increase of the feeling of wellbeing; on the contrary, low carbohydrate intake is associated with more sadness.

Omega-3 and polyunsaturated fatty acids (PUFAs): it was hypothesized that consuming enough long-chain PUFAs is related in preventing depression (Sharma et al., 2023). Omega-3 deficiencies are frequent if fish is not eaten in enough quantities, and risk of depression has been linked to low fish intake. The most lacking are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), whose therapy has been suggested to be effective in depression (Kunugi, 2023).

Between the minerals, the ones related to depression are:

- Iron: patients with iron-deficient anemia have higher rates of anxiety disorders, depression, and sleep disturbances.
- Magnesium: it has an impact on CNS function and have antidepressant and neuroprotective effect.
- Zinc: zinc deficiency may increase cortisol levels, decrease neurogenesis and neuroplasticity, and disrupt glutamate homeostasis, all of which may help in the development of depression (Sharma et al., 2023). In particular, zinc deficiencies induce elevated activity of the HPA axis and glucocorticoid release, and proinflammatory cytokines, causing detrimental effects on the brain (Kunugi, 2023).

1.5 Effects of meal timing and circadian rhythms on depression

Circadian rhythmicity is related to the light exposure during the 24 hours of the day. Cellular clock mechanisms evolved to be sensitive to light. The biological clock is in the suprachiasmatic nucleus and is responsible for the generation and maintenance of the circadian rhythms in the body and regulates different activities (Oosterman et al., 2015).

CNS is not regulated only by light: nutrients, temperature, hormones, feeding/fating state, sleep-wake state, and physical activity are peripheral stimuli for the circadian cycle. Circadian rhythm has an impact on the metabolism on the body, but also metabolic processes can influence the circadian rhythm in a bidirectional interaction.

Food is one of the external synchronizers of the circadian rhythm: meal timing is important (Serin and Acar Tek, 2023).

Timing and composition of the food can cause metabolic disruption of the normal clock output. Fat intake and sugar intake has been associated with disruption of circadian clock. On a molecular level evidence show that fatty acids can alter the circadian molecular clock, both centrally and peripherally. In the same way, timing of glucose intake could be important for normal energy homeostasis. Glucose uptake shows diurnal variation. Glucose can induce cellular circadian rhythms. Changes in glucose blood levels are followed by alterations in hormones like insulin, glucagon, somatostatin, which can affect the clock mechanism. It is not clear if sugar and fats have their own effect on the clock, or if it is due to the alterations they cause in the energy status. Number of calories is possibly more important for photic resetting than the metabolism of a high-fat diet, since a study showed that a hypocaloric diet was shown to speed up resynchronization to a shifted light-dark cycle, while high-fat diet slowed it down (Oosterman et al., 2015).

Misaligned circadian rhythms impact on microbiota. In murine models, a combination of a high-fat diet and circadian disruption leaded to microbial dysbiosis. There is evidence that some bacteria have clock genes that regulate the behavior of their host in a circadian way. Preliminary data suggest that disruption of circadian clock and/or feeding time can directly impact the gut microbiota. In this way it would be possible to use timing of eating to protect against weight gain (Kaczmarek et al., 2017).

Chronotypes are the individual circadian preferences that influence behavioral patterns; there are three main categories: morning, evening, and intermediate types. The one that has more negative consequences is the evening chronotype, which is associated with irregular eating, meal skipping, lower intake of fruits and vegetables and higher intake of drinks and fats, with long-term consequences on cardiometabolic health. Evening chronotype has been associated with higher risk of metabolic dysfunction, diabetes, gastrointestinal disorders, psychiatric symptoms, and even more predisposition to eating disorders. Chronotype may be useful for the prediction of disease outcome (Franzago et al., 2023).

Circadian misalignment is considered a risk factor for obesity and cardiometabolic disease. Even milder changes in timing can cause higher Body Mass Index (BMI), risk of obesity and Type 2 diabetes: consumption of more calories at dinner, later waking time and shifted timing for meal consumption and snacks eaten during the day (Boege et al., 2021).

Especially the evening pattern was related to mood disorders, while the traditional morning type had lower risk of mood disorders. In a Japanese study, patients with depression were more likely to be obese, characterized by having snacks and eating frequently at night, and by less breakfast

consumption. A meta-analysis reported a significant correlation between skipping breakfast and depression (Kunugi, 2023).

Circadian disruption is increasing in modern society due to the electric light at night and the use of technology like smartphones, television and computer screens that are sources of night-time light. Almost the totality of US citizens and more than 80% of all humans face significant night-time pollution. Exposure to light at night causes desynchronization of biological and behavioral rhythms with negative consequences for health. Mood disorders, and major depression in particular, are related to sleep and circadian disruption with irregular light-dark cycle. Not always it easy to maintain a regular light-dark cycle, since in our society sleep timing and duration are often challenged by work or school schedules or social events. Neural systems associated with affect, like the HPA axis, are under circadian regulation, hence the high prevalence of mood disorders in our modern society may reflect the widespread disruption of circadian rhythms (Walker et al., 2020).

High screen time is related to bad sleep in a bidirectional way. Furthermore, epidemiological studies found that looking at screens increases the risk of depressive disorders, even in adolescents and children (Kunugi, 2023).

Human clinical data support this interaction between major depressive disorder and circadian processes. Particularly patients with Major Depressive Disorder (MDD) are often characterized by alterations in sleep/wake states, social rhythms, and hormone rhythms, like melatonin and cortisol. Severity of MDD is also correlated with the degree of circadian misalignment. Even most successful treatments for depression directly affect the circadian rhythms (bright light therapy, wake therapy, social rhythm therapy, and antidepressants). Chronotherapies' efficiency and the diurnal variation in symptoms provide evidence that circadian disruption may underline MDD, even if it is not the only cause, it may be intensifying symptoms in individuals predisposed for mood disorders (Walker et al., 2020). Resetting the central clock in the SNC by exposure to sunlight in the morning and righting the peripheral clock by eating breakfast can help in activating the body and the mind, which is crucial in the treatment of depression (Kunugi, 2023).

1.6 Exercise and depression

Exercise and physical activity are strictly related to depression. People less active are more at risk of developing depression later in life. Daily physical activity has a protective role against depression. Exercise is suggested as a treatment for depression. A randomized controlled trial proved that effects of exercise therapy and antidepressant were similar. Aerobic activities like walking, jogging,

or dancing two to five times a week were included in the exercise schedule: gradually increasing the length of time of exercise, starting from few minutes to 30-40 minutes and increasing the intensity to faster walking. In time also resistance training should be included to improve depression and muscle strength. Exercise was shown to increase BDNF and neurogenesis in the hippocampus in mice; in humans, research results suggest that exercise increases hippocampal volume and suppresses age-related decline.

Outdoor activities in green spaces improve depressive symptoms and have a general positive effect on mental health. Benefits to the mood were seen in gardening and forest bating, traditional practice of Japan, because they provide exposure to green spaces, sunlight and phytoncide (Kunugi, 2023).

A systematic review and meta-analysis found that most effective exercise modalities for depression are walking or jogging, yoga, strength training and dancing. Strength training was more effective in women, while yoga was more effective for men. Among older people yoga was the most effective exercise, while for youngers was strength training. Intensity of the exercise can play a role; in particular, vigorous activity was proven to be more effective. The possible explanation of the positive outcomes is represented by a combination of factors: social interaction, mindfulness or experiential acceptance, increased self-efficacy, immersion in green spaces, neurobiological mechanisms, and acute positive affect. The results indicate that group exercises or a structured program could provide support to achieve better outcomes in depressive symptoms. Interventions should be adapted to individual characteristics such as age, severity of depression, and comorbidities. Health services could use exercise programmes as an alternative or adjuvant treatment for major depression (Noetel et al., 2024).

Physical exercise may have inhibitory effects on inflammation and microglia activation. It has been indagated a possible role of the gut microbiota in mediating the mental health improvement due to exercise in patients with depression. In mice and rats the antidepressant action of exercise was associated with the gut microbiota. Future research is needed to understand better the involvement of inflammatory mediators in a potential exercise-microbiome pathway to alleviate depression (Donoso et al., 2022).

1.7 Vegetarian and vegan diets

Vegetarian diet excludes the consumption of all type of meat and meat products, fish, mollusks, and crustaceans. Based on the presence or not of animal product we distinguish two types of vegetarian diet:

- Lacto-ovo-vegetarianism (LOV): meat exclusion but presence of dairy products, eggs, and honey, beside a great variety of plant-foods. Subcategories are lacto-vegetarian (LV) which excludes eggs, and ovo-vegetarian (OV) which excludes dairy products.
- Veganism (VEG): excludes all products from animal origin including dairy products, eggs, and honey.

The nutritional profiles of both diets vary greatly in relation to types, amounts, and extent of processing of the plant food consumed. For the LOV diet variety is greater, since it also includes animal products (Agnoli et al., 2017).

Proteins in vegetarian diet are a cause of concern, because it is often thought that they are not contained in adequate amounts. Protein quality is determined by the digestibility and amino acid content. Vegetable proteins in soy and gluten have high digestibility, while whole cereals and pulses have lower digestibility due to the presence of pant cell walls and anti-nutritional factors. Anti-nutritional factors can be present or produced by processing or due to genetic modification. Some of these anti-nutritional factors are digestive enzyme inhibitors, tannins, phytate, and glucosinolates. Pulses, cereals, potatoes and tomatoes contain inhibitors of digestive proteolytic enzymes. Soybeans contain trypsin inhibitors, while peas and soybean products contain less amounts of it. Heat treatment, extrusion or removal can inactivate these enzyme inhibitors. Germination of seeds and grains produces enzymes that reduce polyphenol and phytate levels improving protein digestibility. Regarding the essential amino acid content, soy protein are sufficient like animal proteins. Normally the limiting essential amino acid is lysine, especially in cereals, so they must be combined with other sources of vegetable proteins like pulses or oily seeds. In this way the lysine and other essential amino acid intake is sufficient.

Vitamin B_{12} is normally obtained by animal origin products even if in small amounts. Some algae contain this vitamin but often bioavailability is low. Vitamin B_{12} in supplements is normally highly effective in correcting vitamin B_{12} deficiencies. LOV diet can provide vitamin B_{12} in different amounts depending on the type and quantity of animal foods consumed, while for VEG the only reliable sources are fortified foods and supplements. Vegetarians should monitor their vitamin B_{12} status regularly.

Calcium is normally present in plant food, but its bioavailability is inversely proportional to the amounts of oxalate and phytate of the diet, which are abundant in spinach, Swiss chard, and beet leaves. In fortified foods the calcium salts are absorbed with the same ease of the calcium present in cow milk. Calcium used to produce tofu has similar bioavailability of the one in cow milk. To meet recommendation criteria, vegetarians should pay attention on the consumption of good sources of calcium.

Iron is obtained mostly from plant sources even in Italian omnivores. The bioavailability of iron in plant sources is lower. A good way to improve bioavailability of iron is to consume ascorbic acid or other acids found in fruits and vegetables during a meal containing iron. This happens because acid is a chelator and reductor of Fe^{3+}, facilitating the non-heme iron absorption. Iron bioavailability can also be enhanced by using food preparation methods such as grinding, soaking, and germination, and using the sour-dough method to leaven bread. In this way, the phytic acid content of cereals and legumes is lowered and iron sequestration is reduced. Iron-fortified foods can improve iron intake.

Zinc is normally obtained from animal products. For VEG and LOV diets, good zinc sources are represented by cereals, whole grains, pulses, nuts, and seeds. They also contain phytate which chelates zinc limiting its intestinal absorption. Processes like milling, sprouting, soaking, and sour-dough leavening can increase the bioavailability of zinc by activating the endogenous phytates present in phytases present in cereals and pulses.

N-3 fatty acids are limited in plant foods. The only omega-3 fatty acid present in sufficient amounts is the α-linolenic acid (ALA). Main sources of ALA are flaxseeds, hemp seeds, chia seeds, walnuts, and some seaweeds. ALA is an essential fatty acid, from which also eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can be synthesized. EPA and DHA are extremely limited in vegetable foods. ALA elongation to EPA and DHA is limited by the type of diet: inadequate intakes of energy, protein, pyridoxine, biotin, calcium, copper, magnesium, and zinc; high dietary linoleic acid, contained in corn and sunflower oils; and excessive intakes of trans fatty acids and alcohol. Vegetarian can improve their omega-3 intake by consuming good sources of ALA and limiting intake of omega-6 and trans fatty acids, by limiting consumption of processed and deep-fried foods and alcohol.

In conclusion, well-planned and balanced vegetarian diets can provide adequate nutrient intake. Italians can find lot of plant foods traditionally consumed in Italy, and as a personal choice can introduce foods coming from other cultures like soy products, and processed foods like seitan (Agnoli et al., 2017).

Healthy vegetarian diet patterns can be achieved by incorporating plant protein foods. The healthy vegetable diet pattern is high in soy products like tofu and other processed soy products, beans, lentils, nuts and seeds, and whole grains (Apostolakopoulou et al., 2024).

1.7.1 Vegetarian and vegan diets' effect on microbiota

Vegetarian diets impact the gut microbiota. High quantity of fiber could promote the growth of beneficial bacteria in the gut, leading to a healthier microbiota profile and potentially reducing inflammation and oxidative stress (Wang et al., 2024).

Diets low in fiber, high in protein and fat are associated with increased intestinal inflammation and permeability through alteration of the bacterial populations and metabolites that modulate inflammation. Metabolites derived from microorganisms, such as bacteriocins, SCFAs, microbial amino acids, and vitamins play a role in activating the intestinal immune system defending against external pathogens. Dietary patterns can alter both diversity and function of the gut microbiota. Vegan and vegetarian gut microbiota profiles are similar and include several beneficial bacteria, while they both differ from omnivores. In omnivores were found bile-tolerant harmful microorganisms. Animal-based diets usually have higher levels of fecal bile acids, which enable the emulsification of dietary fats and the absorption of lipids and lipophilic vitamins. Bile acids act in several metabolic and inflammatory pathways, altering the composition of gut microbiota. Animal-based diet may also be involved in antimicrobial resistance in the gut microbiota environment, since antimicrobial resistance genes were found less frequently in vegans' microbiota communities. *Prevotella* species are more present in the plant-based dietary habits, while in omnivores *Bacteroides* are predominant. *Bacteroides* are involved in infections providing antimicrobial resistance against a variety of antibiotics, while *Prevotella* seem to play an anti-inflammatory role in certain diseases.

Dietary fibers may influence the type and number of bacterial species. Fermentable dietary fiber is used as a substate by gut microbes to produces bacterial metabolites, including SCFAs with anti-inflammatory properties on the intestine. Indigestible carbohydrates increase *Bifidobacterium* spp. and *Lactobacillus* spp., both associated with a protective role in the human intestinal barrier by inhibiting the invasion and growth of bacterial pathogens.

Bifidobacterium spp. and *Lactobacillus* spp. are increased also by polyphenols, of which vegetarian diets are rich. Polyphenols pass into the colon, where they are metabolized by colonic bacteria, influencing their bioactivity.

Quality and quantity of fat influence the microbiota composition. Vegetarian diets are usually low in fats and contain monounsaturated and polyunsaturated fats, which increase the Bacteroidetes to

Firmicutes ratio. Animal saturated fats on the contrary decrease *Bifidobacterium* spp. and increase Proteobacteria and Firmicutes, which can lead to inflammation and metabolic derangements (Sakkas et al., 2020).

Findings about microbiota composition are limited by several challenges. Microbiota is affected by environmental factors. Antibiotic use, lifestyle, and type of diet are responsible for modification of the human gut microbiota. Also, age affects microbiota composition, since with aging levels of Bifidobacteriaceae decrease. Geographical location also plays a role since different food items are consumed. Studies analyzing microbiota composition in vegan/vegetarian diets compared to omnivores usually did not differ between types of omnivore diets, which should be done in further studies since Western-type of diet is consistently different from Mediterranean diet (Losno et al., 2021).

A study assessed the impact of vegan diet and meditation on microbiota composition and metabolites composition. Participants joined the Samyama Program, a meditation retreat of 8 days, that included a 2-month preparation with vegan diet. At least half of the food required to be consumed raw, and participants were asked to avoid garlic, onion, chili, eggplant, coffee, tea, alcohol, stimulants, and illicit drugs.

In meditators were found changes in the microbial community structure (beta diversity), while no differences in microbial composition (alpha diversity). Meditators were found to have higher abundance of *Lachnospiraceae*, Lactobacillus, and Bifidobacterium. In meditators were present higher levels of branched SCFAs, including iso-butyrate and iso-valerate. *Lachnospiraceae* are linked to SCFA production and can positively influence disease progression for several diseases, including depression. Changes in metabolite profiles and higher proportion of branched SCFA (BCFA) were observed in meditators. Recent evidence suggests that iso-butyrate may improve 5-hydroxytryptophan levels through upregulation of Tryptophan hydroxylase 1, leading to an anti-depressant effect (Raman et al., 2023).

1.7.2 Vegetarian and vegan diets' effect on depression

Fruits and vegetables are rich in antioxidants, especially polyphenols, which decrease depression. Antioxidants can help with protection of the brain from oxidative damage. Nutritional deficiencies in plant foods are associated with an increase in depression symptoms. An epidemiological study showed that vegetarians have lower intake of omega-3 fatty acids, vitamin B_{12} and folic acid, and higher intake of nuts which can be associated with increased levels of omega-6 fatty acids, all causing an increased risk of depression. Several observational studies showed increased risk of depression with low vitamin B_{12} and high homocysteine levels (Apostolakopoulou et al., 2024).

Research about the relationship between depression and vegetarian diets found inconsistent results. Some research suggests that vegetarians have worse depressive symptoms than omnivore, possibly due to abstinence from meat. Meat eaters were associated to lower depressive symptoms than vegetarians. In other studies, it was proven that depression had lower incidence in vegetarians than in omnivores. Inconsistent findings may result from diet quality rather than plant-based dietary pattern. Low-quality foods, especially high in sugar, saturated fats, and refined grain, are also consumed in plant-based diet. This results that low-quality food can be found both in omnivores and vegetarian diets. Results show that high quality plant foods are associated to reduced depressive symptoms, while low quality plant foods are related to increase in depressive symptoms.

Other factors in the vegetarian diet may impact mental health, for example food restriction and food group exclusion. Walsh and colleagues demonstrated the association between high-quality dietary omnivore, vegan and vegetarian diet and decreased depressive symptoms; vegetarian and vegan diets were associated to a higher quality of the diet. The less ultra-processed, refined, and sugary foods are consumed, the more improved depressive symptoms are found (Walsh et al., 2023).

A representative survey in Germany found an association between vegetarian/vegan diet and female gender, younger age, lower BMI, higher depression scores, and higher eating disorder-related psychopathology. Men usually are found to think that meat is essential in a proper diet due to the association between meat and masculinity, so it was expected to find more females to be vegetarian/vegan. The causality between vegetarian diet and depression is not defined. What was found is that in vegetarians is more frequent having eating disorder symptoms. Vegetarian diet was reported to favor fixation on health-conscious eating in orthorexic behaviors, while it also helped individuals with eating disorder to restrict calories and increase feelings of control. Depression and eating disorders are probably not caused by the vegetarian diet, but vegetarian diet may be a symptom or a maintaining factor of the disorder (Paslakis et al., 2020).

A study conducted in China found that in older adults, plant-based diet could be useful for mitigating depressive symptoms, targeting a pertinent aspect of geriatric mental health. Healthcare professionals could in this way offer personalized dietary recommendation in the geriatric care plans, to improve mental health outcomes, together with other activities such as community-based workshop, health education, and interventions within the residential care facilities (Wang et al., 2024).

The mechanism underlying the improvement of mental health with plant-based foods is not defined, but it was suggested that B vitamins and antioxidants may play a role. B_6 and folate are

inversely associated with depression, and supplementation with these vitamins reduced the risk of depressive symptoms. The richness in antioxidants of the vegetarian diet may reduce symptoms via reduction of oxidative stress. Dietary carbohydrates may have a role in depression, by affecting brain tryptophan concentrations and the synthesis of serotonin. Improvement in dietary pattern associated with the vegetarian diet lead also to a better physical health, stimulating individuals to be more physically and socially active, leading to a better emotional change (Agarwal et al., 2015).

1.8 Mediterranean diet

The Mediterranean Diet (MD) was defined by Ancel Keys during the 1960s being low in saturated fat and high in vegetable oils, as observed in Greece and Southern Italy.

The Seven Countries Study associated Mediterranean dietary pattern with reduced risk of coronary heart disease compared to other countries like northern Europe and the United States (Davis et al., 2015). Recent epidemiological studies established that adherence to Mediterranean diet is associated with reduced risk of development of metabolic syndrome, type 2 diabetes, cardiovascular disease and some neurodegenerative diseases and cancer (Bach-Faig et al., 2011).

Twenty-two countries across three continents are presumably contributors of the Mediterranean eating pattern. This results in a variety of possible definitions and not an absolute one (Donovan et al., 2017).

During the following years the definition has evolved from Keys' one.

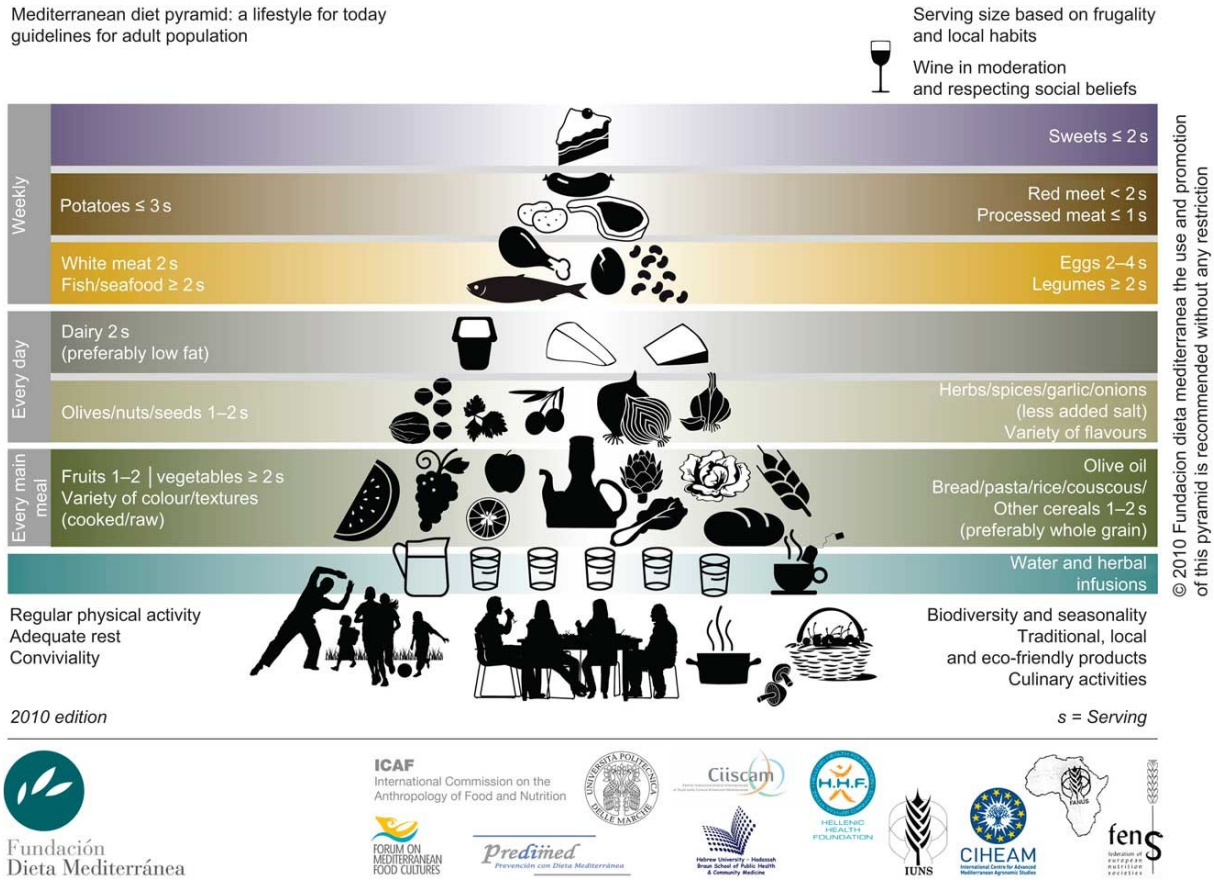
General guidelines include high intake of extra virgin cold olive oil, vegetables including leafy green vegetables, fruits, cereals, nuts and pulses/legumes. Intake of fish and other meat, dairy products and red wine should be moderate, and low of eggs and sweets. There are different definitions regarding quantities and frequency of consumption of these foods (Davis et al., 2015).

In 2010 the Mediterranean Diet was included in the UNESCO Representative List of the Intangible Cultural Heritage of Humanity. Its benefits are associated with decreased morbidity and mortality, but Mediterranean diet comprehends culture and an essential link between people and territories. The cultural heritage can be seen by Countries as an invitation to rediscover their own eating traditions beside the globalization of food industry. The Mediterranean diet should have a universal application since the word diet derives from Greek indicating "lifestyle" not only "list of foods" (Bonaccio et al., 2021).

Several foods of the Mediterranean diet contain bioactive compounds: antioxidants like proanthocyanidins and flavonoids, and omega-3 polyunsaturated fatty acids. Mediterranean diet favors monounsaturated over saturated fatty acids, dietary fibers, antioxidants and phytosterols (Donovan et al., 2017).

A revised Mediterranean Diet Pyramid (Fig. 3) was produced and designed by scientists and experts to have a common representation of the Mediterranean diet in the Mediterranean area and a tool to help adopt a healthier and sustainable lifestyle. This description should be adapted in dietary patterns and portion sizes to the specific country following the various geographical, socio-economic and cultural contexts. The recommendations can be followed by the healthy adult population but should be revised to the special needs of children, pregnant women, and those with health conditions.

Figure 3. The Mediterranean diet pyramid (Bach-Faig et al., 2011)



The dietary pattern indicates the proportions and frequency of consumption of the main foods of the Mediterranean diet. At the base of the pyramid, we find foods that should be consumed more frequently and in larger portions because they have moderate quantity of energy and provide satiety. At the upper levels are foods that should be consumed in moderate quantities and less frequently.

Everyday meals should contain:

- Cereals: preferably wholegrains which contain more fibers and valuable nutrients like Mg, Fe, and vitamins
- Vegetables: raw consumption of at least one serving to ensure vitamin and mineral intakes.
- Fruit: prefer variety of colors and textures to ensure variety of antioxidants and protective compounds

Proper hydration is fundamental to maintain body water equilibrium, this is why is recommended an intake of 1.5-2 liters of water per day, which may vary based on age, physical activity, weather, and health status.

Dairy products should be included in moderate amounts, because they are a source of saturated fatty acids, so are preferred those low-fat and fermented.

Olive oil is a good source of lipids with a high content of monounsaturated oleic acids and abundance of antioxidant compounds. Other good sources of lipids are olives, nuts, and seeds which contain also vitamins, minerals, and fibers.

Spices, herbs, garlic, and onions can be used to increase flavors and palatability to dishes and reducing the use of salt, which is correlated to the development of hypertension in the predisposed individuals.

Weekly consumption of plant- and animal-origin protein is recommended. Fish and shellfish, white meat and eggs are recommended for their high-quality protein content. Combination of legumes and cereals is a good meat alternative as healthy plant protein and lipid source. Red meat and processed meats should be eaten in small quantities, because they are associated with chronic diseases and cancers. Potatoes should be eaten moderately because of their high glycemic index.

In the top of the pyramid there are sweets which are rich in sugars and unhealthy fats, which contain a lot of energy and contribute to weight gain.

As we already mentioned, Mediterranean diet includes cultural and lifestyle elements, which should be preserved to acquire all the benefits it can give.

Socialization and conviviality of meals contribute to strengthening the sociality and identity of the communities. Food is shared between friends and family and supports community feeling. The pleasure associated with the conviviality of meals can improve health status by positively affect food behavior.

Culinary activities need dedicated time and space in everyday meals, celebrations and religious festivals to guarantee the cultural preservation of the Mediterranean diet.

Regular practice of physical activities is fundamental to balance the energy intake, maintain a healthy body weight, and provide several health benefits. Rest should not be forgotten because an adequate night sleep is a fundamental part of the healthy and balanced lifestyle.

Seasonality should be followed to maximize the content of protective nutrients. It is also a way to match the need of having sustainable diets for present and future generations. Another way is to prefer traditional, local, eco-friendly and biodiverse products whenever possible to preserve the Mediterranean landscape and sea. Reducing demand of animal consumption brings to lower demands on soil, water, and energy resources. Agricultural biodiversity represents an important role in varying foods and their micronutrient and phytochemical content (Bach-Faig et al., 2011).

Mediterranean diet is measured through adherence to it, in particular several scores can be used, which are obtained by administration of validated questionnaires. Questions are about types and amount of eaten food. These questionnaires do not focus on the food farming type (organic or conventionally grown), the degree of industrial processing, nor the biodiversity (Bonaccio et al., 2021).

1.8.1 Mediterranean Diet and microbiota

The Mediterranean diet has major health benefits and has also been associated with a positive impact on human microbiota and reduced systemic inflammation. The richness in polyphenols of the Mediterranean diet is a positive characteristic, and polyphenols used as supplements had a positive impact on depression, anxiety, and quality of life in patients suffering from depression. Polyphenols can also modulate the composition of the gut microbiota, by inhibition or stimulation of certain bacteria (Donoso et al., 2022). The Mediterranean diet is characterized by high amounts of fiber and polyphenols, which operate prebiotic action on specific strains. The soluble fibers are fermented by gut bacteria and are used as a source of SCFAs, which have several health benefits: modulation of the immune response, preserving the gut barrier integrity, and regulation of the energy metabolism (Zambrano et al., 2024).

As we already discussed, Western diet is linked to metabolic endotoxemia and microbial dysbiosis. The Mediterranean diet on the contrary seems to promote the reverse effects, which is also attributed to its typical microbiota composition and function. Current evidence confirms the relationship between the Mediterranean diet and the gut microbiota, which has composition and biosynthetic capacity responsive to the diet. The nutrients can modulate the microbiome toward a characteristic probiotic state (Gundogdu and Nalbantoglu, 2023).

The role of gut microbiota in converting food components, such as fiber and polyphenols into anti-inflammatory molecules and signals can positively impact the brain. These components are easily found in the Mediterranean diet (Ross et al., 2024).

In this diet the presence of lean protein sources is positive. It has been shown that high-fat diet leads to microbiota dysbiosis that involves the alterations in the abundance of butyric acid-producing bacteria, opportunistic pathogens, and SCFA-producing bacteria. This dysbiosis can be caused by the metabolism of bile acids, trimethylamine N-oxide (TMAO), and SCFAs due to the fats present in the diet. Microbiota diversity is inversely correlated with a high fat and saturated fatty acid consumption.

The central source of fats in the Mediterranean diet is the olive oil which has been associated to several positive effects on health. Olive oil is rich in tocopherols, carotenoids, and polyphenols. Olive oil can impact the microbiota: its consumption is positively associated with increased presence of *Lactobacillus*, *Bifidobacterium*, and *Clostridium* in gut microbiota. This alterations in the gut microbial community can lead to modulation in inflammatory processes (Zambrano et al., 2024).

The Mediterranean diet has been associated with a beneficial immunomodulatory effect. This benefit is linked to the mediation of the gut microbiota. The interaction between diet, gut microbiota, and immune system occurs through different mechanisms: modulation through dietary-derived microbial metabolites, diet-induced alteration of the microbiota composition, alteration of the fitness of immunomodulatory microbes, and modulation in host metabolism. The first mechanism is partly due to the modulation of the immune and inflammatory responses, including SCFAs, such as butyrate, polysaccharide A and peptidoglycans. In individuals adhering to Mediterranean diet is seen improvement of inflammation biomarkers, including C-reactive protein (Gundogdu and Nalbantoglu, 2023).

1.8.2 Mediterranean Diet and depression

Evidence showed positive correlation between Mediterranean-style diets and improvement in patients with depression. The consumption of fish, fruits, vegetables, and whole grains in the

Mediterranean diet is associated with a lower risk of depression. A healthy nutrition showed a positive association with improved mental health in children and adolescents, while a correlation was found between unhealthy dietary patterns and compromised mental health. The causality between diet and mental health is still not proven. A possible explanation is that unhealthy food is eaten by patients with depression as self-medication, since it temporarily improves mood and stress response (Ross et al., 2024).

Increased consumption of olive oil can reduce the use of other oils, containing omega-6 PUFAs. The ratio of omega-6 and omega-3 PUFAs is higher in Western diets and can contribute to a pro-inflammatory state. Low omega-3 is associated with risk of mental health disorders including depression. The Mediterranean diet with its high content of omega-3 and other essential nutrients represents a benefit for mental health, since nutrients work synergistically in a healthy brain (Parletta et al., 2018).

A review, which included also cross-sectional studies and cohort studies, found a probable beneficial association between healthy eating patterns of the Mediterranean diet and depression. All analyzed studies showed a decreased risk of depression with adoption of the Mediterranean diet. The onset of depression is associated with the mechanisms of inflammation, oxidative stress, insulin resistance and change in vascularity which can be modified by the diet, the Mediterranean diet in particular. The Mediterranean diet includes the necessary amounts of omega-3 fatty acids, B_6 and B_{12} vitamins, magnesium, zinc, and other essential nutrients fundamental to normal functioning. The insufficient intake of these nutrients is related to an increased risk of depression, so deficiencies should be avoided (Apostolakopoulou et al., 2024).

2. Purpose of the study

The purpose of this work is to conduct a systematic review of the available data on the correlation between diet and depression.

The systematic analysis is divided in two parts, for the investigation of two different dietary approaches: vegan/vegetarian diet and Mediterranean diet. The study aims to evaluate the impact of these dietary approaches on psychological well-being, quality of life and depression symptoms.

The expected outcomes of this research include a positive effect of these dietary approaches to improve depressive symptoms and quality of life. These findings could implicate that is possible to improve depression through a personalized nutrition, using diet as a possible adjunctive therapy together with antidepressants.

3. Methods

3.1 Data source

The search was conducted in PubMed database with the available data up to May 8, 2024. The search was focused on identifying clinical trials and randomized controlled trials that examined a correlation between diet and depression.

The research was asked according to the PICO method (Patient problem, Intervention, Comparison, Outcome). In the first research the keywords used were ("Vegan diet" OR "Vegetarian diet") AND (Depression OR "Depressive symptoms" OR "Major Depressive Disorder"). The second research used the keywords ("Mediterranean diet") AND (Depression OR "Depressive symptoms" OR "Major Depressive Disorder").

3.2 Inclusion and exclusion criteria

We included all the trials found regarding vegetarian and vegan diet, while only randomized controlled trial for the Mediterranean diet, written in English. The outcomes reported should regard at least depression symptoms, and at least one of the following: weight loss, psychological well-being and quality of life, or dietary changes.

We included studies regardless of their publication status or size.

We used the PRISMA diagram (Figure 4 and 5) to describe the selection process of the studies, retrieved by the PRISMA 2020 statement (Page et al., 2021).

Figure 4. The selection process of studies following the PRISMA diagram for the vegetarian/vegan diet

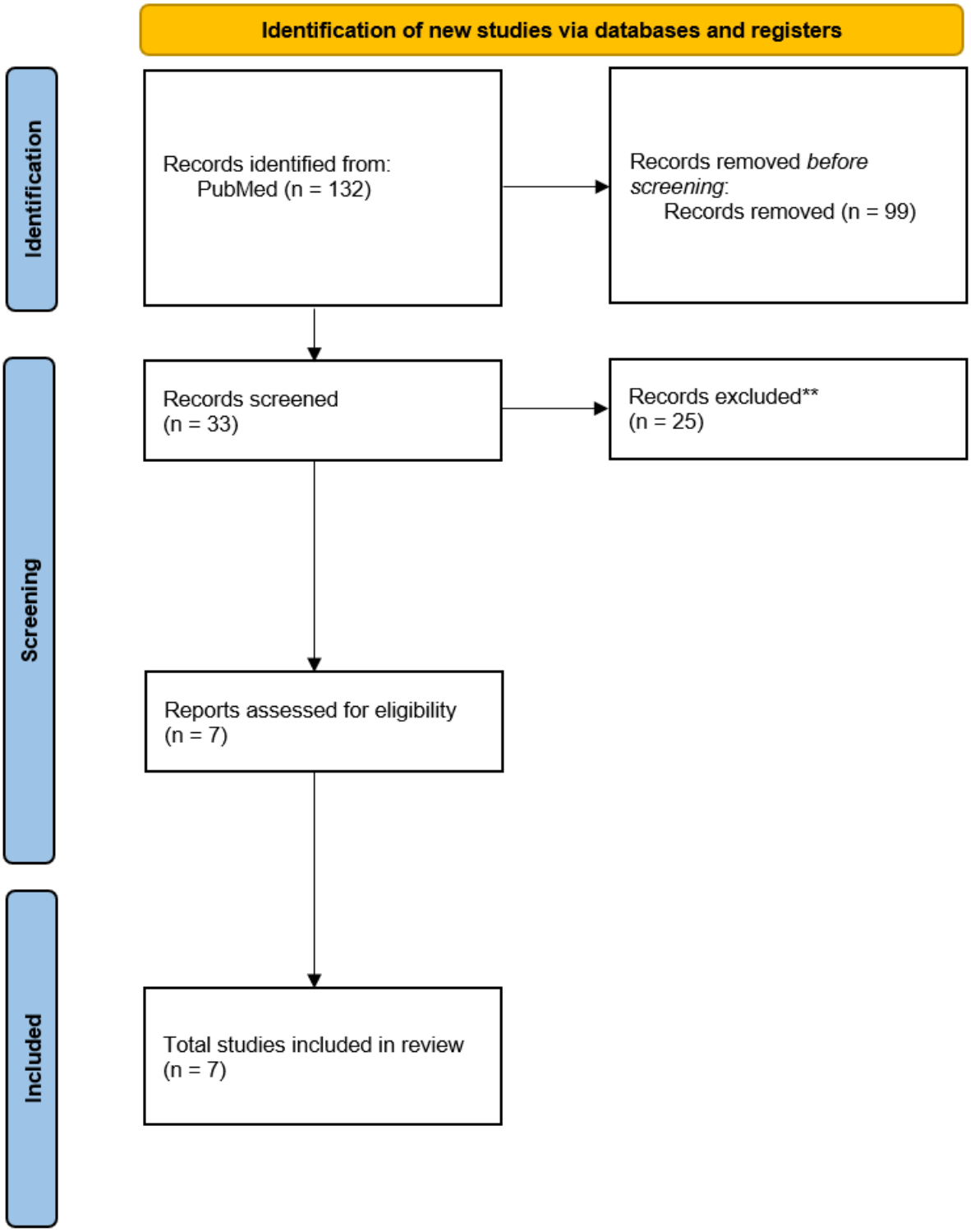
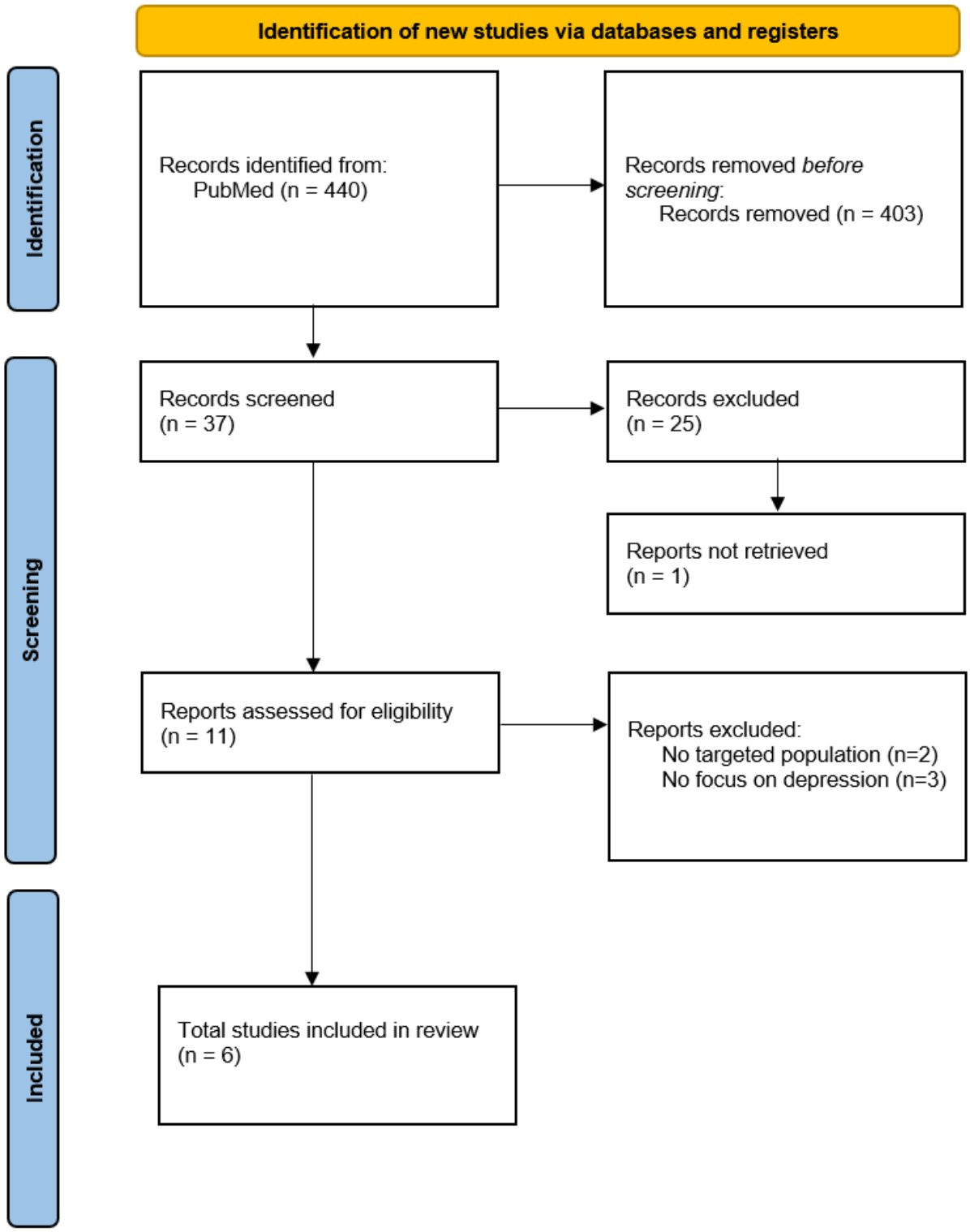


Figure 5. The selection process of studies following the PRISMA diagram for Mediterranean diet



3.3 Data extraction and main outcomes

In addition to the outcomes, the following information was extracted from each study when available: year of publication, country, population, number of participants, mean age, number of females, intervention type and duration, and study design.

3.4 Limitations

The collected studies were characterized by heterogeneity of methodological approaches in design, assessment of outcomes and score to represent them. Moreover, the inclusion of observational trials, often necessitated by the absence of randomized controlled trials, poses inherent limitations in establishing causal relationships. Additionally, some studies featured small participant cohorts, potentially compromising statistical power and the applicability of results. Some studies did not have a control group.

The heterogeneity of the studies through outcome measures, intervention periods and populations precluded a meta-analysis. Several trials had a short duration and no follow-up measurements.

Given these constraints, further studies are needed with more homogeneity of measurements of the outcomes. Careful consideration and extrapolation of our findings to broader contexts are advised.

4. Results – vegetarian diet

Seven studies have been systematically examined that align with our established selection criteria.

In the subsequent table, we have documented pertinent details, encompassing authorship, geographical origin, participant counts (that completed the study), control counts, number of females, mean age, intervention, duration, and the reported outcomes we selected.

Table 1. Description of articles included in the systematic review

Author, Year	Country	Study Design	Population	Intervention group size	Control group size	Number of Females	Mean Age	Intervention	Duration	Outcomes
Link et al., 2008	USA	Prospective observational Study	Adults	51	-	38	53	Hippocrates Health Institute program: strict vegan diet, exercises, psychotherapy	1-3 weeks	QOL improvement (SF-36), lower mean depression score (HADS). Scores improved more in the group following raw vegan diet
Kahlenova et al., 2013	Czech Republic	RCT	Adults with Type 2 diabetes	37	37	39	54.6 ± 7.8	Both groups with hypocaloric diets for 12 weeks: intervention group with vegetarian diet. Last 12 weeks also aerobic exercise	24 weeks	QOL (OWLQOL and WRSM) and mood improvement, lower depression score (BDI). Greater positive effect in the vegetarian diet group
Yu et al., 2014	China	Pilot study	Elderly	44	-	19	65 ± 4.9	DMBI model: Chan practice, mind-body exercises, vegetarian diet and avoid hot and spicy foods. Training session once a week.	12 weeks	Psychological well-being improvement (self-rated), perceived stress score reduction, marginally reduction in depression score (GDS) (only 2 subjects with depression at baseline)
Agarwal et al., 2015	USA	quasi-RCT	Adults with BMI ≥ 25 and previous diagnosis of Type 2 diabetes	94	122	-	43.8	Low-fat vegan diet, instruction and support with nutrition education lectures; vegan menu in the cafeteria	18 weeks	Psychological well-being, depression and anxiety improvement (SF-36). Improvement in work productivity

(Continued on next page)

Table 1 (*continued*)

Author, Year	Country	Study Design	Population	Intervention group size	Control group size	Number of Females	Mean Age	Intervention	Duration	Outcomes
Null and Pennesi, 2017	USA	Behavior modification study	Adults with depression or anxiety	166	-	85	-	Anti-inflammatory plant-based diet with 70% raw and 30% lightly cooked foods. Environmental hygiene, exercise, mindfulness, examination of beliefs.	12 weeks	Large improvement in area of moderate-severe depression (self-reported diary), improvement of insomnia, weight loss
Sadhasivam et al., 2021	USA	Prospective observational Study	Adults	195	59	110	42.2 ± 11.6	Isha Samyama retreat: meditation experience after a preparation of months with vegan diet	8 days	Physical health improvement, weight loss, lower depression scores (CES-D-10)
Haghighatdoost et al., 2023	Iran	Cross-sectional study	Adults	2.033	-	-	-	FFQ to evaluate dietary intakes: different plant-based dietary indices (PDIs). Overall PDI, healthy PDI, unhealthy PDI	-	PDI and hPDI not associated with depression and anxiety (HADS). Highest consumption of uPDI doubled the risk of depression.

QOL, Quality of Life; SF-36, Medical Outcomes Study SF-36; HADS, Hospital Anxiety and Depression Scale; RCT, Randomized Controlled Trial; OWLQOL, Obesity and Weight-Loss Quality of Life; WRSM, Weight-Related Symptoms; BDI, Beck Depression Inventory; DBMI, Dejian Mind-Body Intervention; GDS, Geriatric Depression Scale; BMI, Body Mass Index; CES-D-10, 10-item Center for Epidemiological Studies Depression Scale, FFQ, Food Frequency Questionnaire.

4.1 Quality assessment

The Cochrane evaluation of the risk of bias Tool was used to assess the quality of the two RCTs, which allows rating of the risk (low, unclear, or high) for many types of bias. In these studies, the most frequent risk of bias is the performance and detection bias, since participants were not blinded about the group of belonging.

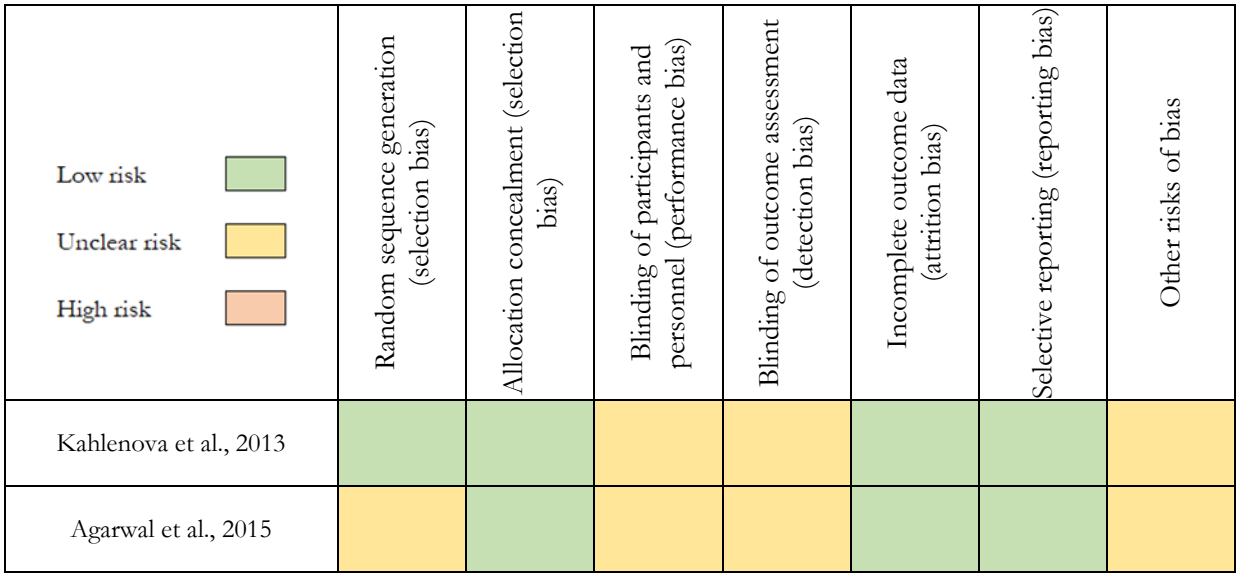


Figure 6. Summary of risk of bias assessment for the Clinical Trial studies.

The quality assessment of the other five studies was conducted using the Joanna Briggs Institute Critical Appraisal tool. This tool is comprised of 11 questions (Moola et al., 2017):

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?
9. Was the follow-up complete, and if not, were the reasons for the loss to follow up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

The most frequent risk of bias in the observational studies was the absence of control groups. Another risk of bias is represented by the short duration of the follow-ups, and the high rates of dropout, which precluded an analysis on the long-term effects of the interventions.

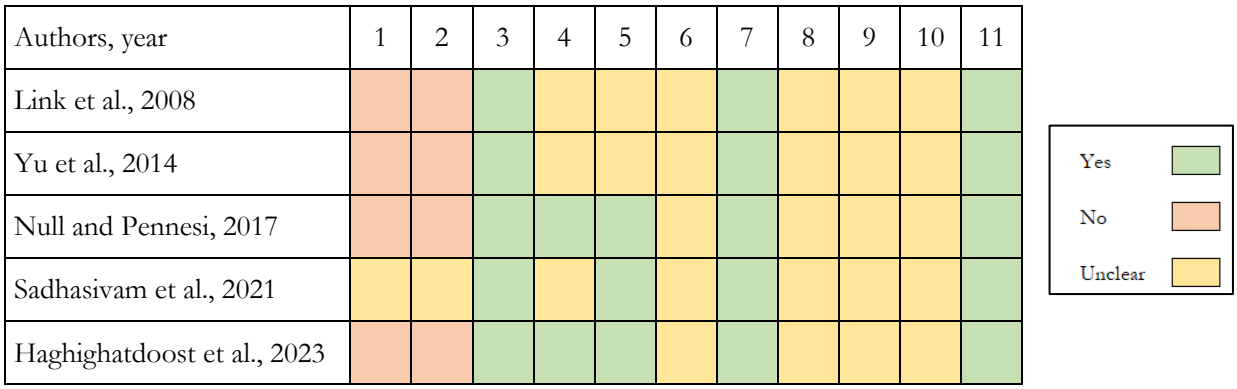


Figure 7. Summary of risk of bias assessment for the Clinical Trial studies.

4.2 Study characteristics

4.2.1 Location and sample size

Four of the studies were undertaken in the USA, the other studies were conducted in Czech Republic, China and Iran. The seven studies examined included a total of 2,620 participants with sample sizing raging between 37 and 2,033 individuals. Including also the control groups, the total number of participants was 2,838.

4.2.2 Population characteristics

All studies' targeted population was adults ≥18 years. In a study the population included elderly men and women aged 60-83 years (Yu et al., 2014). A study was conducted with adults with Type 2 Diabetes (Kahlenova et al., 2013), while other adults previously diagnosed with Type 2 Diabetes or with BMI ≥ 25 (Agarwal et al., 2015).

4.2.3 Study aims

Link et al. (2008) aimed at understanding how quality of life, depression, stress and anxiety change after a stay at a raw vegan institute.

Kahlenova et al. (2013) investigated the effects of a calorie-restricted vegetarian and conventional diabetic diets alone and in combination with exercise on insulin resistance, visceral fat and oxidative stress markers in subjects with Type 2 Diabetes. In the trial they assessed also quality of life, depression score and eating behavior in response to a vegetarian and conventional diabetic diet aiming at understanding if the vegetarian diet leads to an improvement in quality of life and mood.

Yu et al. (2014) conducted a study that aimed to explore the potential benefits of the *Dejian* mind-body intervention (DMBI) for psychological and physical health in older Chinese adults.

Agarwal et al. (2015) wanted to determine whether a dietary change to a plant-based nutrition improves depression, anxiety and productivity in a multicenter, corporate setting.

Null and Pennesi (2017) aimed to examining the effects of a plant-based diet, lifestyle and behavior modification program on patients affected by chronic moderate to severe depression and anxiety and a range of other chronic conditions.

Sadhasivam et al. (2021) had the objective of assessing physical and emotional well-being before and after Samyama retreat, by evaluating psychological surveys and objective health biomarkers.

Haghighatdoost et al. (2023) sought to examine the association between dietary indices, depression and anxiety in a large multicentric sample of Iranian adults.

4.3 Summary of findings

Eight papers were selected based on the predetermined criteria and subsequently analyzed to assess their respective outcomes.

In three studies participants were provided of dietary instructions to help them follow better the dietary intervention (Kahlenova et al., 2013, Agarwal et al., 2015 and Null and Pennesi, 2017). Three different questionnaires to assess dietary intake were used, ASA24 (Agarwal et al., 2015), FFQ (Haghighatdoost et al., 2023), and Three-Factor Eating Questionnaire (Khalenova et al., 2013), otherwise none was used.

A study analyzed plant-based food to assess its degree of healthiness and to find if there is an association between type of plant-based food and depression. It was not a trial in which participants changed their habits with a vegetarian dietary intervention, so its findings have limited use (Haghighatdoost et al., 2023).

Some interventions included a program of meditation or similar activities to help relaxing the mind or reaching a state of mindfulness (Link et al., 2008, Yu et al., 2014, Null and Pennesi, 2017, and Sadhasivam et al., 2021).

Depression was measured with several scales in the used papers. Hospital Anxiety and Depression Scale (HADS) was used by Link et al. and Haghighatdoost et al.; 36-Item Short Form Health Survey (SF-36) was used by Link et al. and Agarwal et al.; Geriatric Depression Scale (GDS) was used by

Yu et al.; Beck Depression Inventory (BDI) was used in Kahlenova et al. study; 10-Item Center for Epidemiology (CES-D-10) was used by Sadhasivam et al.; in the Null and Pennesi study a self-report diary was used.

Quality of life was measured in four studies. Link et al. and Agarwal et al. used the SF-36 survey both for depression and quality of life assessment. Yu et al. used a self-rated health question "generally speaking, how is your health: very good, good, fair, poor, or very poor?". Kahlenova et al. assessed quality of life through two questionnaires: Obesity and Weight-Loss Quality of Life (OWLQOL) and the Weight-Related Symptoms (WRSM).

4.4 Type of studies and intervention

In the study designed by Pennesi and Null, the diet described was anti-inflammatory, with 70% raw and 30% lightly cooked plant-based foods. Several foods were eliminated: refined carbohydrates, animal products, caffeine, alcohol, and artificial additives. Fruits and vegetables juices were included in the recommended foods. Recipes were given to the participants to help them follow the protocol better, and nutritionist were available to assist them (Null and Pennesi, 2017).

Agarwal et al. (2015) designed a study which was quasi-randomized because the sites of the corporate were assigned randomly to the intervention or control groups, but the participants in it were not randomly selected since the randomization was done by site rather than individuals. The intervention group was characterized by dietary intervention and weekly group meetings with instruction and support. The program included a low-fat vegan diet, with particular attention in avoiding added oils, and favoring foods with a low glycemic index. Participants were given daily supplements of multivitamin to meet B_{12} requirements. An additional help in following the diet was presented by the cafeteria menu which presented low-fat vegan options in the intervention sites, while in the control sites no other foods were added in the cafeteria menu (Agarwal et al., 2015).

Kahlenova et al. (2013) designed a 24-week randomized control trial conducted on people with Type 2 diabetes treated by oral hypoglycemic agents. The protocol included a calorie-restricted vegetarian diet that was given to the intervention group, and a hypocaloric conventional diet to controls. Caloric intake was based on the measurement of resting energy expenditure individually. Vegetarian diet consisted of 60% calories from carbohydrates, 15% protein and 25% fat and the only allowed animal product was a portion of low-fat yogurt a day. All meals were provided. Both

groups were supplemented with B_{12} vitamin. Alcoholic beverages were limited to one for women and two for men. In the first 12 weeks participants were asked not to change their habits of physical activity. In the last 12 weeks aerobic exercise was added based on an individualized exercise program (Kahlenova et al., 2013).

In a study conducted in China, it was explored if the DMBI method can be used to improve physical and psychological health in older Chinese adults. DMBI stands for *Dejian* mind-body intervention which is based on the Chinese tradition. It combines *Chan* practice for self-awareness and psychosocial education with mind-body exercises and a dietary modification with a vegetarian diet and avoidance of hot and spicy food which according to the Chan principle would generate excessive internal heat with negative consequences on mood and physical health (Yu et al., 2014).

An observational study conducted in a raw vegan institute explored the changes in quality of life, stress, and depression after at least a week of stay in the institute. The method included following a strict vegan diet with majority of food is eaten raw, exercises and stress reduction activities, psychotherapy and other complementary therapies. People who attend there are guest of the institute more than patients and go there to improve their general health, paying for the stay. This is why attendees' health ranges from very healthy to very ill. Participants were selected and asked to complete a questionnaire at the beginning of their stay and then in a 12-weeks follow-up (Link et al., 2008).

A similar study was conducted on meditators of Samyama program by Sadhasivam et al. The Samyama program includes a preparatory process in the two months before the program, in which participants are asked to follow a vegan diet with at least 50% of the food consumed raw. Other recommendations included to avoid foods considered negative to life energy like garlic, onion, chili, eggplant, asafetida, coffee, and tea. Participants were discouraged to use alcohol, stimulants, illicit drugs and to smoke cigarettes. The preparatory process comprised also a practical part made of daily practices of *hata* yoga for physical posture, *kriya* yoga for breathing and sound, and *Shoonya* meditation for conscious non-doing. During the program, participants remain silent for the 8 days of the program. Control had no specific instructions and did not practice meditation. To the purpose of the study, depression, anxiety, vitality, mindfulness, joy, and resilience were measured to understand how the scores change in different timing: T1 at baseline (5-8 weeks before Samyama), T2 in 0-2 weeks before Samyama, T3 2-6 weeks after Samyama, and T4 3-4 months after Samyama. Part of the participants did also blood measurements at the same timepoints to assess changes of hemoglobin, lipid profile and C-reactive protein (Sadhasivam et al., 2021).

The cross-sectional multicentric community trial of Haghighatdoost et al. (2023) had the objective to find a correlation between type of plant-based food and depression and anxiety. The composition of the plant-based diet is like a pro-vegetarian one[2]. It was used the Food Frequency Questionnaire to assess the dietary intake of the participants. Plant-based Dietary Indices (PDI) were divided into three categories: overall PDI, healthy PDI (hPDI), and unhealthy PDI (uPDI). Unhealthy foods consisted of fruit juices, potatoes, refined grains, sweets, and desserts. The mental health assessment was made using the Iranian version of the Hospital Anxiety and Depression Scale (Haghighatdoost et al., 2023).

4.5 Weight loss

In the trial with Type 2 Diabetes participants, weight loss was greater in the intervention group that followed a vegetarian diet. Both groups had hypocaloric diet and exercise but in the intervention group results were greater. Also, waist circumference and volume of subcutaneous fat decreased in both groups but greater in the intervention one. This was due to the caloric restriction but in the case of the vegetarian diet decreased the feeling of hunger and participants were less likely to overeat (Kahlenova et al., 2013).

In Sadhasivam et al. study, mean body weight decreased after the preparation process but even more after 3-4 months after the Samyama program (T3) (Sadhasivam et al., 2021).

4.6 Psychological health

Pennesi and Null reported an improvement in insomnia symptoms in those participants who were affected before the study following the plant-based diet and protocol of exercise, environmental hygiene and mindfulness and de-stressing techniques. Also, their sociality improved: while before they were in isolation mood, they looked for social interactions and they noticed a more optimistic mentality (Null and Pennesi, 2017).

The Agarwal and colleagues' study took place in a large corporate environment and evaluated the physical and emotional well-being with the 36-Item Short Form Health Survey (SF-36). It found a general improvement in the intervention group significantly greater than in the control group. Also work productivity was assessed with the Work Productivity and Activity questionnaire - General

[2] The term is referred to the pro-vegetarian diet described by Martínez et al., which is represented by a food pattern characterized by a progressive approach to vegetarianism, with progressively portions of plant-derived foods and reduction of animal-derived foods (Martínez et al., 2014)

Health version (WPAI-GH), which included questions about impaired productivity at work due to health problems. Improvements were greater in the intervention group rather than the controls (Agarwal et al., 2015).

In older population it was found an improvement in psychological well-being: reduction of the score of perceived stress, and a decrease in sleep disturbances. A general health improvement was measured by improvement in the self-rated health from the beginning and post-intervention (Yu et al., 2014).

In Link et al. study, quality of life was measured with the Medical Outcomes Study SF-36. Generally, quality of life improved after the stay at a raw vegan institute from baseline to the 12-weeks follow-up. Most of the improvement was mental quality of life. The attendees were divided in two groups: a group was not following the raw vegan diet at the beginning at the study but at the end was, the second one did not follow the diet at the end of the study. Comparing their results, the first group scored better in every SF-36 category. Overall well-being improvement was found in the group adhering to the raw vegan diet, also in the scores for anxiety and perceived stress. The benefits of the institute were probably linked to the self-renewal mood of being on vacation more than a health care intervention, but that improvement was reported even after two months from leaving the institute (Link et al., 2008).

After the Samyama program, it was found an overall psychological improvement. Anxiety decreased in all participants with a medium effect size; in those who had baseline anxiety it decreased greater than in those without clinically significant anxiety. Mindfulness increased but with small changes. Joy increased after the preparatory phase but had no significant changes in the later timepoints. Vitality had a medium effect over time with an increase until the T3 and then remained similar in the follow-up. Resilience increased with a significant effect of time but after T3 remained similar. In the control group there were no significant changes in the scores over the entire period (Sadhasivam et al., 2021).

Kahlenova et al. found that between the participants, the intervention group that followed the vegetarian diet had a greater improvement in quality of life and mood than the control group. The depressive symptoms measured by the Beck Depression Inventory did not reach the score of thresholds but had an improvement from the beginning anyway (Kahlenova et al., 2013).

4.7 Depression symptoms

In Pennesi study, participants reported an improvement in depressive symptoms: 62% a large improvement or remission of symptoms, while the other part moderate or small; only 12 participants noticed no change. 78% of the participants of Pennesi's study after 6 months reported they were able to decrease or eliminate antidepressant under indication of their physicians (Null and Pennesi, 2017).

In Agarwal et al. study, depression was assessed in the SF-36 test and was found improved in the intervention group (Agarwal et al., 2015).

In Yu et al. study there was a minimal improvement in depression with the DBMI protocol, probably due to the low number of participants with clinical depression, which were only two people (Yu et al., 2014).

Depression in Link et al. study did not reach the minimum of the abnormally symptomatic which is set to 33: at baseline the depression mean score was 22.7 out of 100, which improved to 20.7 when measured in the 12-weeks follow-up. The decrease of depression score was not significant. Like for the overall well-being, improvement was greater in the group that was following the raw vegan diet (Link et al., 2008).

The Samyama program had significant results in reduction of depression. Depression was measured by the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10). In this study, 17 participants had baseline scores significant for depression. They had significantly higher scores at T1 compared with other assessments and significantly lower scores at T3. Participants without baseline depression at T1 had significantly lower scores at T3. Overall, participants had decreased scores at T3 with a medium effect. The decrease in scores between T1 and T2 (time of the preparation to Samyama retreat) was higher in those with baseline depression. T4 scores of those with baseline depression were similar to T2 but lower than the clinical cut-score for depression and did not go back to baseline levels (Sadhasivam et al., 2021).

Considering the Plant-based Dietary Indices (PDI), in the study of Haghighatdoost et al., a correlation between unhealthy PDI and higher risk of depression and anxiety was found. The overall PDI and healthy PDI did not provide significant data of association with depression. Finally, there were no findings about healthy plant-based foods and reduction of depression in their study population (Haghighatdoost et al., 2023).

5. Results – Mediterranean Diet

Six studies have been systematically examined that align with our established selection criteria.

In the subsequent table, we have documented pertinent details, encompassing authorship, geographical origin, participant counts (that completed the study), control counts, number of females, mean age, intervention, duration, and the reported outcomes we selected.

Table 1. Description of articles included in the systematic review.

Author, Year	Country	Study Design	Population	Intervention group size	Control group size	Number of Females	Mean Age	Intervention	Duration	Outcomes
Sánchez-Villegas et al., 2013	Spain	RCT	Adults at CV risk	2739	1184	2003	67	PREDIMED trial: nutritional intervention. 2 MD: one with supplement of extra virgin oil and one of nuts. Education to follow MD, control group advice on low-fat diet.	3 years	No significant decrease in depression risk (HR). Restricting to patients with type 2 Diabetes and MD-+nuts, 40% reduction of depression risk compared to control.
Jacka et al., 2017	Australia	RCT	Adults with depression	33	34	48	40.3	SMILES trial: nutritional consulting sessions by a clinical dietitian, with goal setting, mindful eating. Indication about foods. Food hamper. Control group befriending sessions	12 weeks	Improvement in depression scores (HADS and MADRS) in dietary support group greater than controls. Improvement in anxiety. Improvement in food consumption, less unhealthy items.
Parletta et al., 2018	Australia	RCT	Adults with depression	75	77	105	44 ± 13	HELFIMED trial: MedDiet cooking workshops, food hampers, and fish oil supplements	6 months	Greater improvement in DASS-21 depression scores in intervention group; improved mental health-related QOL (AQoL-8D) with improved diet

(Continued on next page)

Table 2 (continued)

Author, Year	Country	Study Design	Population	Intervention group size	Control group size	Number of Females	Mean Age	Intervention	Duration	Outcomes
Bayes et al., 2022	Australia	RCT	Young males (18-25) with clinical depression	36	36	0	22	AMMEND trial: dietary intervention by a clinical nutritionist: personalized dietary advice, goal setting, mindful eating to adhere to MD. Control group: befriending support sessions	12 weeks	Improvement in depressive symptoms (BDI) in the MD group. Improvement in quality of life: physical and psychological health (WHOQOL)
Cabrera-Suárez et al., 2022 and 2023	Spain	RCT	Adults in remission from depression	93	103	144	51	PREDIDEP trial: remote nutritional intervention with team of registered dietitians. Free extra-virgin oil.	2 years	Increase in quality of life (SF-36) in patients in intervention group. Improvement in depressive symptoms (BDI). No differences in depression recurrence risk after 2 years.
Gómez-Gómez et al., 2023	Spain	RCT	Adults from PHC centers	1264	1267	1369	58.13	MHBC intervention to promote adherence to the MD, physical activity and/or smoking cessation in attenders of the PHC centers. Control no changes	12 months	No effects in preventing onset of MDD with symptoms at baseline. No differences between intervention and control group regarding depression symptoms (PHQ-9) at 12-months follow-up

RCT, Randomized Controlled Trial; CV, Cardiovascular; MD, Mediterranean Diet; HR, Hazard Ratio; HADS, Hospital Anxiety and Depression Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; DASS-21, Depression Anxiety Stress Scale; AQOL-8D, Assessment of Quality of Life questionnaire; BDI, Beck Depression Inventory; WHOQOL, World Health Organization Quality of Life assessment; SF-36; MHBC, Multiple Health Behavior Change; PHC, Primary Health Care; MDD, Major Depressive Disorder; PHQ-9, Patient Health Questionnaire.

5.1 Quality assessment

The Cochrane evaluation of the risk of bias Tool was used to assess the quality of the RCTs, which allows rating of the risk (low, unclear, or high) for many types of bias.

Risk of bias for most studies is unclear or high for what regards blinding, since participants knew if they belonged to the intervention or control groups. Also, staff was in most studies aware of the group of belonging of the individuals. For this reasons, detection bias and performance bias were high or unclear. Outcomes were reported with low risk in most cases. Randomization was computer generated or by independent personnel, reducing at minimum the risk of selection bias.

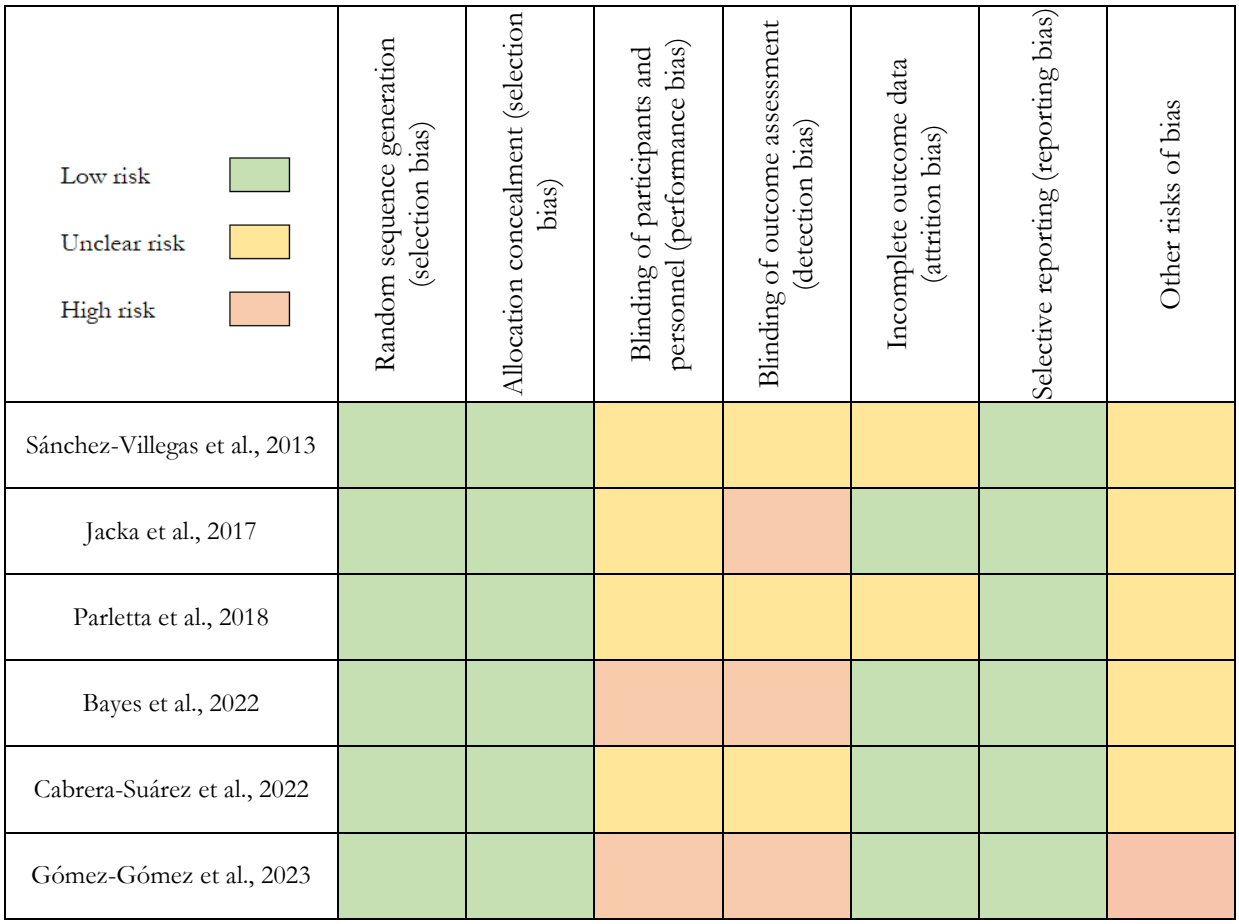


Figure 7. Summary of risk of bias assessment for the Clinical Trial studies.

5.2 Study characteristics

5.2.1 Location and sample size

Three of the studies were undertaken in Spain, the other studies were conducted in Australia. The six studies examined included a total of 4240 participants in the intervention groups, with sample sizing raging between 33 and 2,739 individuals. Including also the control groups, a total of 6941 people took part of the trials. A study included only young males (Bayes et al., 2022) while the total of participants was composed by 52,86% of female.

5.2.2 Population characteristics

All targeted population included adults with ≥18 years of age. A study included adults aged 55 to 80, at high cardiovascular risk. Were included people either with Type 2 diabetes or at least three of the cardiovascular risk factors: current smoking, hypertension, low-density lipoprotein cholesterol >4.110 mmol/l, high-density lipoprotein cholesterol <1.034 mmol/l, overweight/obesity, or a family history of premature coronary heart disease (Sánchez-Villegas et al., 2013). In two trials the targeted population included adults suffering from depression (Jacka et al., 2017 and Parletta et al., 2018). A study targeted young people aged 18 to 25 with clinical depression (Bayes et al., 2022). In a trial participants were adults in remission from depression, and the focus was the quality of life after recovery (Cabrera-Suárez et al., 2022). An intervention trial targeted adults which were treated in Public Health Centers (Gómez- Gómez et al., 2023).

5.2.3 Study aims

The PREDIMED (*PREvención con DIeta MEditerránea*) study aimed to assess the effects of a Mediterranean-type diet on cardiovascular disease. Included in the trial were people with Type 2 Diabetes or at least 3 cardiovascular risk factors. In this setting it was also possible to investigate the effect of the Mediterranean Diet on the risk of developing depression (Sánchez-Villegas et al., 2013).

In the SMILES (Supporting the Modification of lifestyle In Lowered Emotional States) trial the aim was to investigate the efficacy of a dietary improvement program for the treatment of major depressive disorder, hypothesizing that a dietary support could be superior in improving depressive symptomology rather than a social support control condition (Jacka et al., 2017); similarly, in the HELFIMED (Mediterranean-style dietary intervention supplemented with fish oil) trial the aim was to show that healthy dietary changes are achievable and if supplemented with fish oil can improve mental health in people with depression (Parletta et al., 2018). The AMMEND (A Mediterranean Diet in MEN with Depression) study aimed to show that in young males with

moderate to severe major depressive disorder, nutritional counseling can help improve depressive symptoms (Bayes et al., 2022). Analyzing remission from depression, in the PREDIDEP (*PREvención con DIeta Mediterránea de DEPresión*) trial the aim was to improve adherence in recovered patients to improve quality of life (Cabrera-Suárez et al., 2022); another analysis of the PREDIDEP trial aimed at assessing if the dietary intervention could reduce recurrence risk of depression and improve depressive subsyndromal symptoms (Cabrera-Suárez et al., 2023). The EIRA study aimed to assess if a Multiple Health Behavior Change (MHBC) intervention, that promotes Mediterranean diet, physical activity, and/or smoking cessation, is effective in preventing depression in primary care attenders aged 45-75 years (Gómez- Gómez et al., 2023).

5.3 Summary of findings

Six papers were selected based on the predetermined criteria and subsequently analyzed to assess their respective outcomes.

In all analyzed studies participants were provided of consulting sessions to help them following the Mediterranean diet and improve their adherence scores (Sánchez-Villegas et al., 2013, Jacka et al., 2017, Parletta et al., 2018, Bayes et al., 2022, and Gómez-Gómez et al., 2023). A trial provided online consulting sessions instead of in-presence (Cabrera-Suárez et al., 2022).

In five studies food hampers were given to the participants to encourage adherence to Mediterranean Diet: with foods belonging to the MD (Jacka et al., Parletta et al., Bayes et al.), with oil (Cabrera-Suárez et al.), and with oil or nuts based on the type of dietary intervention group (Sánchez-Villegas et al.).

To assess diet quality and the frequency of food groups intake at baseline were used food frequency questionnaires (Jacka et al., and Cabrera-Suárez et al.), the Simple Dietary Questionnaire (SDQ) by Parletta et al., and the Commonwealth Scientific and Industrial Research Organization (CSIRO) by Bayes et al.

To measure the adherence to the Mediterranean Diet were used the Mediterranean Diet Adherence Screener (MEDAS) score (Cabrera-Suárez et al. and Bayes et al.), and the 14-item MedDiet questionnaire (Sánchez-Villegas et al., Parletta et al., Gómez-Gómez et al.), and its variant 11-item questionnaire by Jacka et al.

Every study used a different method to assess depressive symptoms. Sánchez-Villegas et al. (2013) used the hazard ratio to measure the risk of developing depression. Jacka et al. (2017) used the

Montgomery-Åsberg Depression Rating Scale (MADRS) to assess changes in depressive symptoms at baseline and after 12 months, and the Hospital Anxiety and Depression Scale (HADS) was administered as a self-report questionnaire. In a study was used the Depression Anxiety Stress Scale (DASS) to exclude from the trial those without a 'moderate' to 'severe' score, and then to assess improvements during the trial (Parletta et al., 2018). Cabrera-Suárez et al. (2022) and Bayes et al. (2022) used the Beck Depression Inventory to assess depressive symptoms. A study used the Composite International Diagnostic Interview (CIDI) to exclude people with Major Depressive Disorder at baseline and then to evaluate the effectiveness of the intervention on the cumulative incidence of depression and measured the presence and severity of depressive symptoms with the Patient Health Questionnaire-9 (PHQ-9), a self-reported questionnaire with 9 items (Gómez-Gómez et al., 2023).

Quality of life was assessed inn four studies with different scales. Parletta et al. (2018) used the Assessment of Quality of Life (AQoL)-8D which is a 35-item questionnaire on eight dimensions, whose scores can be combined to create a total AQoL-8D score. Cabrera- Suárez et al. (2022) used the SF-36 questionnaire to assess the health-related QOL (HRQOL). Bayes et al. (2022) used the World Health Organization Quality of Life Assessment (WHOQOL) form, with 26 questions on the individual perception of health and well-being over the previous 2 weeks. Gómez-Gómez et al. (2023) assessed quality of life at baseline as information about the population with the EQ-5D-3L questionnaire.

5.4 Type of studies and intervention

All the analyzed studies were randomized controlled trials in which the participants were randomly assigned in 1:1 ratio.

The only study which had three different dietary interventions was the PREDIMED trial in which participants were randomly assigned in a 1:1:1 ratio: to the low-fat diet of the control group, to the MD with EVOO, or to the MD with nuts for the two intervention groups. The two MD groups received indication to follow the Mediterranean diet following recommendations, and free supplemental food: 1 l/week EVOO for one and 30 g/day of mixed nuts to the second one. At baseline was assessed the individual scores of adherences to the MD using the 14-item questionnaire, and based on the results, personalized dietary advice was given to participants to improve their scores. The control group received only advice to follow a low-fat diet and nothing about MD. To encourage adherence small non-foods gift were given. No advice about energy restriction or physical activity were given. Every three months, individual interviews and group

sessions were conducted by dietitians, which consisted of informative talks and written material with descriptions of typical foods, seasonal shopping lists, meal plans, and recipes (Sánchez-Villegas et al., 2013).

The SMILES trial included participants with a diagnosis of major depressive episode (MSE), scored 18 or more in the MADRS, and had a poor dietary quality before the enrollment. If under antidepressant therapy or undergoing psychotherapy, participants were required to be under the same treatment for at least 2 weeks prior to randomization. The dietary intervention involved personalized dietary advice and nutritional counselling support by a clinical dietitian. During the sessions, participants received motivational interviewing, goal setting and mindful eating, in order to support optimal adherence to the recommended diet. In this case the recommended diet was the 'Mod*i*MedDiet', based on the Australian Dietary guidelines and the Dietary Guidelines for Adults in Greece, focused primarily on increasing diet quality by supporting the consumption of 12 key foods groups: wholegrains, vegetables, fruit, legumes, low-fat and unsweetened dairy foods, raw and unsalted nuts, fish, lean red meats, chicken, eggs, and olive oil. At the same time the aim was to reduce the intake of foods like sweets, refined cereals, fried food, processed meats and sugary drinks, and alcohol, the only one that could be consumed beyond 2 standard drinks per day was wine, red or white. The Mod*i*MedDiet is composed of protein for 18% of total energy (E), fat 40% of E, carbohydrates 37% of E, alcohol 2% of E, fiber/other 3% of E. The diet was designed to be easy to follow, sustainable and satiating, and could be consumed *ad libitum* because the focus was not the weight loss. Participants received individual dietary support sessions. At the first session the dietitian conducted a food frequency questionnaire to assess usual dietary intake and diet quality. Participants were provided with a brochure about the intervention to receive support in achieving dietary adherence. Food hampers with the components of the diet, recipes and meal plans were given to the participants. They were also encouraged to set personalized goals in the subsequent sessions which had the focus on motivate them. The social support control condition followed a befriending protocol, participating to sessions in which they discussed with trained staff about neutral topics like news, music, or sports (Jacka et al., 2017).

In the HELFIMED study, participants were adults between 18 and 65 years of age and diagnosed or self-reported depressive symptoms over the previous 2 months or longer. Participants were asked to continue with their treatment for depression if they were treated, but not to start a new therapy for the 6-months duration of the study. The intervention group was given a fish oil supply for three months. The first visit included a nutrition education session held by a dietitian, nutritionist and support study staff. In the subsequent visits, participants of the MedDiet group took part in cooking workshops with recipes focused on simple, affordable and tasty meals with

Mediterranean-style dietary principles. In these occasions food hampers with ingredients for the recipes were given, including extra virgin olive oil, vegetables, fruit, legumes, tomatoes, tuna and nuts. The control group undertook social activities with snacks provided (Parletta et al., 2018).

The AMMEND study's population consisted of young males aged 18-25 already diagnosed with MDD by a general medical practitioner, with a score ≥20 on the 21-item Beck Depression Inventory II, representing a moderate to severe depression. They also scored ≤40 on the Commonwealth Scientific and Industrial Research Organization (CSIRO) diet survey, which consists of questions regarding quantity, quality, and variety of the foods consumed. The participants under treatment could continue their therapy but it had to be the same for at least two weeks prior the study. The intervention started by an appointment with a clinical nutritionist that gave a personalized dietary advice, motivational interviewing, goal setting, and mindful eating to support optimal adherence to the Mediterranean diet. The used MD followed the dietary guidelines of Greece and Spain. The primary focus was to increase diet quality with fresh wholefoods and reducing intake of energy-dense, nutrient-poor foods like sweets, fried food, processed meats, sugary drinks which were limited to less than 3 serving per week. Participants were provided with a flyer with all nutritional information and meal plans, recipes, and with an online daily diet history survey. They also received a food hamper with a selection of Mediterranean foods. The control group received befriending support sessions in which participants talked about neutral topics of interest like movies, hobbies, and sports, and they were given a gift card at completion of the program (Bayes et al., 2022).

The PREDIDEP study used a method similar to the PREDIMED trial and involved dietitians with experience in it. It included participants with previously at least one depressive episode and in a stage of clinical remission. The dietary intervention was conducted remotely through internet or phone by registered dietitians. In the first session participants received explanation about Mediterranean Diet and why it is important to follow it and set an achievable goal (Sánchez-Villegas et al., 2019). Intervention group participant received extra-virgin olive oil for free. Every 3 months participants received written information on Mediterranean foods and seasonal shopping lists, recipes and menus, discussed with the dietitians. No nutritional intervention is comprised in the control group, and subjects received an incentive at trial termination to prevent from withdrawal (Cabrera-Suárez et al., 2022).

In the EIRA study participants were patients in the Primary Health Care (PHC) centers and the intervention comprehended a multiple health behavior change (MHBC): Mediterranean diet adherence, physical activity, and/or smoking cessation. The intervention was administered by

trained PHC professionals, with a maximum duration of 12 months and at individual, group and community levels. The individual plan to promote behavior change was implemented based on the patients' readiness to change. In addition, personalized SMS were sent to promote Mediterranean diet adherence, physical activity and/or smoking cessation. Group intervention were 90-120 minutes sessions to promote MHBC and patients was encouraged to take part of community-type activities such as walks, dance workshops, and healthy cooking workshops. The participants belonging to the control group received usual care. Patients with already major depressive disorder at baseline were excluded since the aim was to understand if MHBC intervention can prevent risk of depression (Gómez- Gómez et al., 2023).

5.5 Dietary changes

The intervention group in the SMILES trial had a positive change in the consumption of several food: wholegrain cereals, fruit, dairy, olive oil, pulses, and fish. A significant decrease in consumption of unhealthy food was shown, while there were no changes in the social support group. The ModiMedDiet score confirmed the improvement in the adherence to the Mediterranean Diet in the dietary intervention group while not significantly in the control group (Jacka et al., 2017).

In the HELFIMED study the intervention group showed an improvement in the total Mediterranean diet score from baseline to 3 months. The participants increased the consumption of vegetables, fruit, wholegrain foods, nuts, and legumes; they lowered intake of unhealthy snacks, meat and chicken. Sweetened drinks were less consumed both by the intervention and the control groups with not significant differences (Parletta et al., 2018).

In the EIRA study a positive change in diet was shown in the intervention group compared to the control group (Gómez- Gómez et al., 2023).

In the AMMEND study the MEDAS score was used. Participants documented all meals and snacks during the time of the study in a widget on their mobile phone. At baseline both groups had similar values for MEDAS. At week 6 and 12 an improvement in the MD group was shown, while no differences in the befriending group (Bayes et al., 2022).

5.6 Weight loss

None of the analyzed study focused on weight loss so the outcomes were not related to weight and BMI.

In the PREDIMED trial participants of all three groups had a marginal decrease in body weight and in waist circumference after 5 years. The intervention was with no calorie control and high-fat so there was no significant change in body weight and some evidence showed an increase in central adiposity compared to the control group (Estruch et al., 2019)

In the SMILES trial the diet intervention was *ad libitum* and did not have a weight loss focus. In fact, BMI did not vary from baseline to the 12-week measurement (Jacka et al., 2017).

5.7 Depression symptoms and psychological health

In the PREDIMED trial, an inverse association with depression was seen in participants assigned to the MD-nuts group, but it was not significant. Both MD groups results were not associated with a decrease in depression risk. Restricting the analysis to the participants with Type 2 diabetes, those belonging to the MD-nuts group showed a stronger and significant reduction in the risk of depression compared to those of the control group. In the 3-years follow up, no significant reduction was found between those with the lowest adherence to MD and those with the highest adherence to MD in the risk of developing depression. During the follow-up period 224 new cases of depression were identified (Sánchez-Villegas et al., 2013).

In the SMILES trial the intervention group had a greater improvement than the control group in depression symptoms according to the MADRS score. At 12 weeks, 10 people of the dietary support group and 2 of the control group achieved remission criteria. From baseline to 12 weeks, the dietary support group improved also in the HADS scale with subscales of both depression and anxiety. Regarding mood disturbance and self-efficacy or well-being, there were no significant differences between the two groups. The Mod*i*MedDiet score improvement was associated with the depression score improvement in the dietary intervention group. Regarding data about psychopharmacological therapy: two patients in the social support group stopped their therapy, while one person per group started taking pharmacological medication in the 12 weeks period of the study. These data were available only for 53 individuals, that are too few to carry out statistics from them. Improvements in depressive symptoms were independent from weight loss (Jacka et al., 2017).

In Parletta et al. study, in both control and intervention groups mental health improved on all scores. Over the first 3 months, the intervention group showed a greater improvement in the DASS depression score and in the quality of life. These changes were persistent also at six months. The better quality of the diet was correlated with a better mental health. Adherence to Mediterranean

diet was associated with lower depression, anxiety, negative emotions, and stress, and overall quality of life with higher positive emotions, better coping and happiness. Reduced intake of takeaway food and unhealthy snacks was associated with improved mental health. The fish oil supplement had also an impact, which was assessed through measurement of erythrocyte omega-3 and omega-6 PUFAs. There were some findings regarding an improvement of mental health with increased omega-3 PUFA eicosapentaenoic acid (EPA), increased omega-3 PUFA docosahexaenoic acid (DHA), and decreased omega-6 PUFA arachidonic acid (AA). A reduced ratio between AA and EPA associated with better pain, senses and physical health quality of life scores at 6 months. Regarding depression, there were no significant findings between increased omega-3 and improved depressive symptoms; depression improvement was associated to a decreased ratio of AA to EPA. Improved depression was also associated with increased Mediterranean diet scores. In both groups an improvement of mental health, probably thanks to the social part of the study, the culinary activities and conviviality which represented an adaptation to the Mediterranean diet lifestyle and cultural elements (Parletta et al., 2018).

In the AMMEND study, both groups improved their BDI-II scores, but with a greater change in the intervention group. At the end of the study, all 36 participants of the MD group witnessed an improvement of their symptoms, and 12 of those (36%) reported a final BDI-II score between 0 and 10, representing a low or minimal depression.
Also, quality of life showed an improvement in MD group compared to befriending one, regarding physical and psychological health. In particular, were found improvements in concentration, sleep, and energy. Fatigue, troubles in sleeping and concentrating are common in depression. In the domains of social relationships and environment the improvement was similar between the two groups (Bayes et al., 2022).

In the first year of intervention of the PREDIDEP trial, the dietary intervention group improved in vitality and mental summary components, the control group did not but the difference between the two groups was not statistically significant. In the 2 years-follow-up mental summary component and vitality improved significantly in the MD group, while no changes in the control group. Statistically relevant was the difference between intervention and control group for what concerns vitality. Also, in general health the intervention group showed improvement already in the first year and then in the second-year follow-up. The intervention group had an improvement in quality of life associated with the Mediterranean diet (Cabrera-Suárez et al., 2023a). Depression recurrence was assessed with clinical evaluations by psychiatrists and clinical psychologists; the subsyndromal depressive symptoms indicate presence of moderate symptoms but do not meet the diagnostic criteria for major depression. Risk of recurrence was calculated with the hazard ratio.

After two years of intervention there were no significant changes in the intervention group regarding the risk of depression recurrence. Depressive symptoms improved in the intervention group after four months, eight, and twenty months of intervention, with significant differences between intervention and control groups Cabrera-Suárez et al., 2023b).

In the intervention group of the EIRA study, the diet behavior improved greatly. The smoking and physical activity behaviors showed an improvement but not statistically significant. Despite the behavioral improvements, no effect was observed in preventing the onset of major depression at the 12-months follow-up. The intervention was not effective in reducing the depressive symptoms at the 12-months follow-up, with no significant differences between control and intervention groups. No evidence regarding the improvement of behavior regarding diet, smoking and physical activity associated with a decrease in depression symptoms neither a prevention of the onset of major depression. The MHBC intervention was not effective in PHC centers to reduce depression (Gómez- Gómez et al., 2023).

6. Discussion

Depression is a disorder with high impact on social and individual level. It is important to understand the factors which increase the risk of developing depressive disorder. Evidence suggests a role of the microbiota-gut-brain axis, in particular alterations in the gut microbiota composition are associated with depression. Physical activity can improve directly depression or indirectly by improving the composition of the gut microbiota (Donoso et al., 2022). Circadian processes also interact with depression disorder, since depression is often accompanied by alterations in sleep/wake cycle (Walker et al., 2020). Meal timing and nutrients impact circadian rhythmicity: a negative association between high fat and sugar consumption and metabolic disruption of the normal circadian clock (Oosterman et al., 2015).

According to several findings, diet has an important role in preventing and treating depression. Diet is considered a modifiable risk for depression, depending on the type of eaten food (O'Neil et al., 2022). Healthy diets and physical activity implementation are considered a good choice for everyone, but the aim of this systematic review was to understand if diet can be used as an adjuvant in treating depressive disorder.

Findings about vegetarian and vegan diets are heterogeneous. The studies varied in design, populations, and specific interventions but shared a common focus on the psychological benefits of plant-based nutrition. Vegetarian/vegan diets were associated with improved depression, quality of life and psychological health in all analyzed studies. Intervention included also meditation (Link et al., 2008; Yu et al., 2014; Null and Pennesi, 2017; Sadhasivam et al., 2021) which may have had a role in improvements of depression symptoms. Improvements were associated also with weight loss, which can impact on depression because of overall improvement of social life, due to overweight-related stigma (Paris et al., 2024). In plant-based foods can be present also unhealthy items: Haghighatdoost et al. (2023) found that unhealthy plant-based indices are correlated with higher risks of depression, whereas overall and healthy PDI did not show associations with depression. When considering vegetarian diet and especially the vegan diet, attention should be paid on possible nutritional deficiencies of omega-3, vitamin B_{12}, and folic acid which may increase depression risk.

Components of the diet may improve gut microbiota composition, resulting in a healthier microbiota profile and reducing inflammation and oxidative stress (Wang et al., 2024), leading to also better depressive symptoms.

Limitations of studies regarding vegetarian diets include performance and detection biases due to the lack of blinding of participants. Short follow-ups limited the ability to assess long-term effects of the interventions. Attrition bias may be present in the studies due to high dropout rates.

This systematic review suggests that vegetarian and vegan diets, particularly when combined with other lifestyle modifications like exercise and mindfulness, can positively influence psychological health by improving quality of life and reducing symptoms of depression. However, variations in study design, intervention specifics, and the presence of biases, underscore the need for more rigorous, long-term RCTs to confirm these findings and better understand the mechanisms involved.

Mediterranean diet in the analyzed study showed a positive effect in improving depression symptoms and quality of life. The association between improvement in adherence to Mediterranean diet and decreased depressive symptoms was evident in four analyzed studies (Jacka et al., 2014; Parletta et al., 2018; Bayes et al., 2022; Cabrera-Suárez, 2023). Improvements were seen without a decrease in body weight, leading to the hypothesis that the beneficial effects of the diet were in the components of the diet and not related to the weight loss. Components are beneficial both for improvement in brain function and for the positive effects on the gut microbiota.

Two studies found that Mediterranean diet did not decrease the risk of developing depression (Sánchez-Villegas et al., 2013; Gómez- Gómez et al. 2023).

Mediterranean diet shows possibilities of improvement of depressive symptoms and quality of life in some populations, but results are inconsistent across different study designs and participant groups. Factors such as study duration, specific dietary interventions, and participant characteristics may influence outcomes.

Limitations include the presence of biases of performance and detection, due to the non-blindness of participants. Potential cofounding variables could affect the interpretation of results. Results are difficult to generalize due to heterogeneity of participants demographics, intervention protocols, and outcome measures.

Further research, potentially with larger sample sizes and longer follow-up periods, is needed to establish clearer conclusions on the effectiveness of the Mediterranean diet in managing depression and improving mental health.

The results of both systematic reviews propose to integrate dietary counseling and diet recommendations in the clinical practice, to complement antidepressants and psychotherapy for depression and enhance overall mental health outcomes.

7. Conclusions

It is known that depression, a common mental disorder, negatively impact on several aspect of daily life. Depression is a complex disorder influenced by biological, psychological, and social factors. Understanding the interactions between the gut-brain axis, nutrition, circadian rhythms, and physical activity is essential for developing effective prevention and treatment strategies.

We analyzed vegetarian/vegan diet and Mediterranean diet, which are both considered healthy diets. Association between healthy diet and improvement of depression is demonstrated by several studies but high-quality clinical trials in well-controlled study populations are needed to prove causality.

Diet is considered a modifiable risk factor for depression. Vegetarian and vegan diets have been associated with improved depression, quality of life, and psychological health, with some benefits potentially arising from meditation and weight loss. However, unhealthy plant-based foods may increase the risk of depression. Studies on these diets have limitations, and more rigorous and long-term studies are needed to confirm these findings. The Mediterranean diet has shown positive effects on depression symptoms and quality of life, attributed to its beneficial components, that improve brain function and gut microbiota. However, results are inconsistent. The studies also have limitations, including biases, potential confounding variables, and participant heterogeneity. More extensive research is needed to establish clearer conclusions.

Considering the findings, the suggestion is to use dietary counselling, considering vegetarian or Mediterranean diets, to implement antidepressants and psychotherapy to improve mental health and depression in particular.

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