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SVEUČILIŠTE U RIJECI
ODJEL ZA BIOTEHNOLOGIJU
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Laura Šlajhert

Utjecaj mediteranske prehrane na depresiju

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Abstract:

The World Health Organization estimates that 3.8% of the world population is affected by some sort of depressive disorder. Major depressive disorder is diagnosed if a person has depressed mood and/or anhedonia for a long period of time, along with at least four other depressive symptoms such as feelings of guilt or worthlessness, lack of energy, poor concentration, appetite changes, psychomotor retardation or agitation, sleep disturbances, or suicidal thoughts. The Mediterranean diet is a mostly plant-based diet, focusing on vegetables, fruits, nuts, beans, whole grains, fish, olive oil and other healthy fats, dairy in smaller amounts, herbs and spices, and moderate intake of red wine. It has been linked to overall improvement of mental and physical health. Some studies suggest that it helps prevent or lower the symptoms of a major depressive disorder. This thesis investigated those studies to gather information from around the world, by the means of different methods, and determine whether most studies do find a connection between the Mediterranean diet and a decrease in depressive symptoms. The results showed that it does generally have a positive effect on lowering depressive symptoms, but they also pointed out the problems with the methods of the studies mentioned, and the need for future investigation of the problem.

Key words:

Mediterranean diet, major depressive disorder, depressive symptoms, depressive disorder treatment, treatment by diet

Sažetak:

World Health Organization procjenjuje da 3.8% svjetske populacije boluje od nekog oblika depresivnog poremećaja. Veliki depresivni poremećaj dijagnosticiran je kada osoba ima anhedoniju i/ili je depresivnog raspoloženja dug period, uz još barem četiri simptoma poput osjećaja krivnje ili bezvrijednosti, manjka energije, slabe koncentracije, promjene apetita, psihomotorne retardacije ili agitacije, poteškoća sa snom ili suicidalnih misli. Mediteranska prehrana je prehrana većinski na bazi biljaka s fokusom na povrće, voće, orašaste plodove, cjelovita zrna, ribu, maslinovo ulje i ostale zdrave izvore masti, manje količine mliječnih proizvoda, začinskog bilja i umjerene količine crnog vina. Povezuje se s cjelokupnim poboljšanjem fizičkog i mentalnog zdravlja. Neka istraživanja predlažu da pomaže spriječiti ili smanjiti simptome velikog depresivnog poremećaja. Ovaj rad prikuplja ta istraživanja kako bi se pregledale informacije sa svih strana svijeta, uz raznolike metode istraživanja, i definiralo postoji li zaista u većini slučajeva poveznica između mediteranske prehrane i smanjenja depresivnih simptoma. Rezultati su pokazali kako generalno postoji pozitivan utjecaj mediteranske prehrane na smanjenje depresivnih simptoma, ali također su istaknuli probleme s korištenim metodama i potrebu za budućim, dubljim istraživanjima problema.

Ključne riječi:

Mediteranska prehrana, veliki depresivni poremećaj, simptomi depresije, liječenje depresivnih poremećaja, liječenje prehranom

Contents

1. Introduction

1.1. Major depressive disorder

Major depressive disorder (MDD) is one of the main causes of disability globally. There are multiple types of depressive disorders, and the World Health Organization (WHO) estimates 3.8% of the population is affected, or 280 million people worldwide (1). According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) (2), it is diagnosed when a person has depressed mood and/or anhedonia causing an occupational or social impairment, and at least four more of these symptoms: feelings of guilt or worthlessness, lack of energy, poor concentration, appetite changes, psychomotor retardation or agitation, sleep disturbances, or suicidal thoughts, for a continuous period of at least two weeks. It is a multifactorial disease, caused by environmental, psychosocial, genetic, and biological factors altogether. Diagnosis is classically done either using the DSM, or the International Classification of Diseases codes (ICD) (3). MDD is caused by disturbances in neurotransmitter activities (like serotonin, norepinephrine, and dopamine) that cause problems in more complex neuroregulatory systems and pathways. To diagnose the severity of symptoms of the MDD, various scales and questionnaires are used for self-assessment or are done by a professional. A patient's clinical history includes their family history, social history, and substance use history. It is important to make sure that no other physical condition can account for the depressive symptoms (4). The studies mentioned in this thesis look variously at MDD and/or depressive symptoms more generally. Those symptoms can be the same as in diagnosed MDD, but during the beginning of their occurrence or not enough symptoms in total for the person to be diagnosed with MDD yet.

1.2. The Mediterranean diet

The Mediterranean diet (MedDiet) is a diet originating from countries bordering the Mediterranean Sea. There are multiple versions of it, which vary slightly, but the European Office of the WHO, Oldways Preservation and Exchange Trust, and Harvard School of Public Health introduced the MedDiet Pyramid where they presented the most common food groups from the diet and their proportions. It also emphasizes the importance of physical activity and the social aspect of eating with others (Figure 1). As the pyramid shows, the diet is mostly plant-based, focusing on vegetables, fruits, nuts, beans, whole grains, fish, olive oil, dairy in smaller amounts, herbs and spices, and moderate intake of red wine. The focus is on healthy fats: olive oil, fish oil, avocados, and nuts, while replacing margarine and butter. The preferred protein source is fish, at least twice a week, and red meat is limited to a few times a month (5).

Studies have shown that a MedDiet helps prevent cardiovascular disease (6). A study on people with diabetes and risk of heart problems showed that a MedDiet supplemented with nuts and fish oil, lowered their chances of death by stroke by 30% compared to a control group assigned to a low-fat diet (7). It has also been shown to influence aging by causing telomeres to decrease in length more slowly, meaning slower aging, in women (8). It causes more healthful aging, with a lower risk of chronic diseases, and longer lifespan (9).

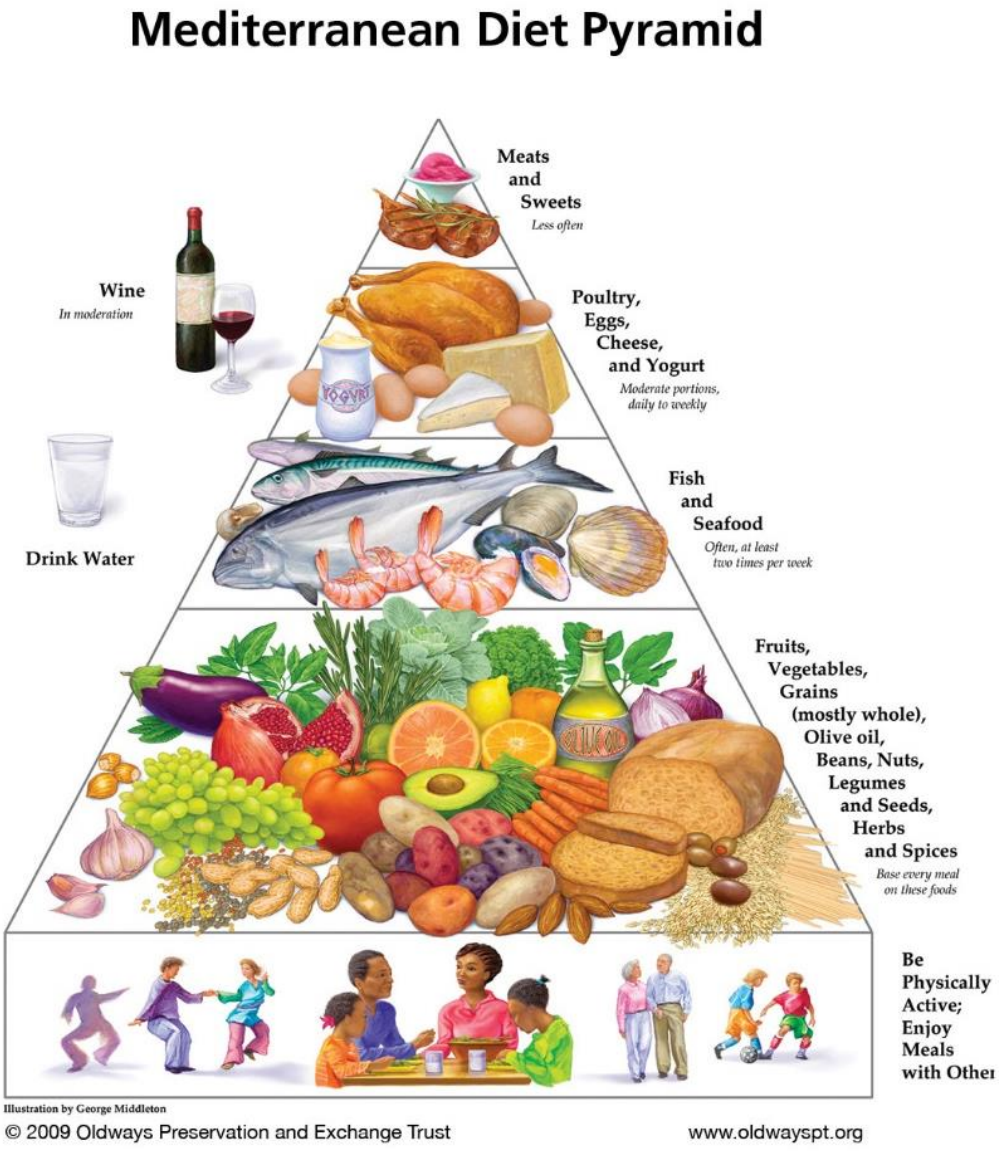

Figure 1. The Mediterranean Diet Pyramid adapted from Oldways (10).

1.3. The Mediterranean diet and mental well-being

There have been many studies that have researched the connection between the mind and the diet, some of which focused on the MedDiet and how it affects mental well-being. These studies suggested that a MedDiet, focusing on olive oil and nuts, improves cognition, and protects against age-related cognitive decline because of the antioxidant and anti-inflammatory properties found in those nutrients (11). It was also concluded that people who practiced a MedDiet for 4 weeks had lower anxiety and negative mood levels than those on other diets (12). It was noticed that following a MedDiet improves mood in general, and decreases depression, tension, confusion, and anger in an Australian sample (13). Higher fish intake, which is a characteristic of the MedDiet, also seems to improve cognition in elderly people over the course of 12 weeks of additional intake (14).

All these facts considered, a literature review was necessary to answer the question does a MedDiet improve mental health, in terms of lowering depressive symptoms or preventing an MDD, using different methods and looking at different populations, rather than keeping it closed off to a small number of people with many similarities.

2. Aims of this review

Through this review, the goal is to gather information from all studies investigating the impact of the MedDiet on depression (both MDD and depressive symptoms more generally) or prevention of depressive symptoms. It is interesting to see whether the benefits come from specific nutrients in the diet or the MedDiet as a whole. The studies included in this thesis focused on different populations and areas of the world. This makes it more accurate and rules out the possibility that some populations naturally have a lower chance of developing depressive symptoms not related to their diet, or if their diet was already mostly focused on the MedDiet and the protective effect existed before the study. After reviewing the papers, it should be possible to conclude whether the MedDiet truly does make a difference and affects the severity of depressive symptoms or is the information insufficient and is there need for further studies.

3. Studies investigating the MedDiet and depression

To date, several population-based research studies have directly addressed the issue of whether a MedDiet effects MDD. Some of them only focused on self-assessment, while others measured micronutrient levels as well, to investigate which nutrients might be lacking to cause or enhance depressive symptoms. These will be discussed in turn, in order of decreasing number of participants.

In many studies, symptom severity was measured using one or more standardised questionnaires or scales. These are summarised in table 1.

Table 1. Major questionnaires and scales used to assess depressive symptoms in studies, in order they were mentioned.

Questionnaires and scales	Abbreviation	Reference
Hospital Anxiety and Depression Scale	HADS	(15)
Geriatric Depression Scale	GDS	(16)
Composite International Diagnostic Interview	CIDI	(17)
Inventory of Depressive Symptomatology	IDS	(18)
Beck Anxiety Inventory	BAI	(19)
Fear Questionnaire	FEAR	(20)
Mini International Neuropsychiatric Interview	MINI	(21)
Beck Depression Inventory	BDI	(22)
Depression Anxiety Stress Scales	DASS	(23)
Positive and Negative Affect Schedule	PANAS	(24)
Hamilton rating scale for depression	HAM-D	(25)
Clinical Global Impression Scale	CGI	(26)
Center for Epidemiological Studies Depression Scale	CES-D	(27)
Patient Health Questionnaire	PHQ-9	(28)
Mini-Mental State Examination	MMSE	(29)

3.1. Studies focusing on clinically diagnosed depression or MDD

A study on 49,261 Swedish women aged 29-49 began with each of them answering the food frequency questionnaire (30). Scores were either 0 or

1, depending on the adherence to a MedDiet. If a woman was consuming foods from a food group typical for a MedDiet, at least in the amount set as the cohort median, her score would be 1, while if she did not consume foods from that same group, or did consume foods not typical for a MedDiet, her score was 0. Based on the number of different food groups a woman consumes, the scores were summed up and the total could be between 0 and 9, indicating low (0-3), medium (4-5), or high (6-9) adherence. This scale was proposed by Trichopoulou et al. (31). The same scale was often used in other studies. Other lifestyle, medical history and demographic factors were also considered. Clinical diagnosis of depression was identified using the Swedish revision of the ICD (3). Both broader and narrower definitions of diagnosis results were considered. The broader definition considered only clinical diagnosis of depression or only dispense of selective serotonin reuptake inhibitors (SSRIs), while the narrower definition considered both together. The study took place over the course of 20 years with two follow-ups, one after 10 years, and the other after 20. When adherence to MedDiet and other lifestyle factors were compared, women with higher adherence tended to be more physically active, older, non-smokers, of higher educational level, and with higher daily energy intake. The results of the study show that with the increase of adherence on the scale 0-9, each higher unit was correlated with a 5% lower risk of developing a depressive disorder. Since older women showed higher adherence to a MedDiet, this suggests an accumulative beneficial effect of a MedDiet on mental health. The association was also stronger when the narrower definition of depression was considered, rather than the broader one. Severe depression notably had the strongest correlation.

Another study on 9670 participants focused on B vitamins and ω-3 fatty acids, important nutrients contained in a MedDiet, and their protective role on MDD, rather than the MedDiet in general (32). Vitamins B12 and B6 are found in dairy and fish, both important parts of a MedDiet, and

they act as cofactors to enzymes in the process of turning homocysteine to methionine and cysteine. Methionine is a reactant in many processes involving neurotransmitters, so if intake of vitamins B12 and B6 is not sufficient, it may cause depressive symptoms because of a lack of monoamines in the brain. Folic acid, or vitamin B9, is an important factor in biopterin-dependent neurotransmitter synthesis, and its deficiency can cause insufficient synthesis of serotonin, dopamine, and norepinephrine (33). ω-3 long-chain polyunsaturated fatty acids (PUFA) cannot be produced in the body and need to be a part of our diet, in a MedDiet it mostly comes from fish, seafood, and oils. ω-3 fatty acids inhibit proinflammatory cytokines, who's excessive production has been linked with depression (34). A food frequency questionnaire was used to assess the dietary habits and exposure to B12, B6, folic acid and ω-3 fatty acids. MDD was assessed based on whether the participants have ever been diagnosed with MDD or if they had ever taken antidepressant medication. Other lifestyle habits were also assessed through a questionnaire. The results showed that when it comes to men, higher folic acid intake had a protective effect against MDD, especially among smokers. With women the results were different, B12 vitamin and ω-3 intake was related to a lower chance of developing depression, especially among smokers and physically active women, while intake of B6 vitamins and folic acid had no impact on the prevalence of depression.

A study on 3923 elderly people aged 55 to 80 with high risk of cardiovascular disease was conducted to determine if a MedDiet would have a protective effect on clinically defined depression (35). A food frequency questionnaire was used to measure their dietary habits, other lifestyle factors were also considered. They were divided into 3 groups; those practicing a low-fat diet, those practicing a MedDiet supplemented with nuts, and those practicing a MedDiet supplemented with olive oil. After the follow up, there were no significant results to suggest that a MedDiet had a protective effect against depression.

A cross-sectional study on 3172 Iranian adults from 18 to 55 years old aimed to discover the correlation between a MedDiet, clinical depression, anxiety, and overall psychological distress (36). A food frequency questionnaire and the Trichopoulou scale (31) were used to determine their dietary habits and adherence to a MedDiet. The Hospital Anxiety and Depression Scale (HADS) (15) was used to determine their mental state and the General Health Questionnaire (GHQ) (37) determined psychological distress. The results showed that overall mental well-being was better with higher adherence to a MedDiet, depression and anxiety were both 40% less probable if a person had a higher score on the Trichopoulou scale. More specifically, fruits, nuts, and dairy were inversely associated with the MedDiet, while grains had a positive association.

Over the course of 6 years, a study was conducted on 2718 older people from 22 Mediterranean islands (38). Clinical assessments were made, dietary habits questioned by a food frequency questionnaire and adherence to a MedDiet measured by a MedDietScore proposed by Panagiotakos et al. (39). The Geriatric Depression Scale (GDS) (16) score was used to determine depressive symptoms. Participants who had more depressive symptoms tended to be less educated, less physically active, living alone, had lower HDL (high density lipids) and LDL (low density lipids) cholesterol levels, and lower adherence to a MedDiet. When they were divided in groups of under and over 80 years old, the results stayed the same, with a higher adherence to a MedDiet associated with a protective effect against depressive symptoms.

A research study on 1634 adults in the Netherlands researched how 238 food items affect depression and anxiety disorders using a food questionnaire, a diagnostic interview Composite International Diagnostic Interview (CIDI) (17), and questionnaires to check depression and anxiety disorders' symptoms and severity: The Inventory of Depressive Symptomatology (IDS) (18), the Beck Anxiety Inventory (BAI) (19), and the Fear Questionnaire (FEAR) (20)(40). Other lifestyle factors were

considered. The scores showed that food items considered to be included in the MedDiet; vegetables, fruit, non-refined grains, and moderate drinking were linked with fewer or no depressive and anxiety symptoms. Even non-drinkers had a higher chance of developing symptoms. The study based its results on the overall lifelong habits of participants, instead of determining a period to see the effects before and after implementing this diet.

A study on 273 patients with MDD was conducted to research how adherence to a MedDiet affects their depression outcome (41). Their disorder was determined by the Mini International Neuropsychiatric Interview (MINI) (21), and depression severity by Beck Depression Inventory (22). Adherence to a MedDiet was calculated by the Mediterranean Diet Adherence Screener (MEDAS) (42). In this study, low adherence to a MedDiet did not mean the prognosis of a participant would worsen, but there was an inverse correlation between a MedDiet and MDD at baseline. Further on in the study, response to depressive symptoms was associated rather with normal weight and lack of metabolic syndromes.

Another study measured the effect of a MedDiet supplemented with fish oil on 152 people aged 18-65 who already self-reportedly deal with depression (43). Their state was confirmed using the Depression Anxiety Stress Scales (DASS) (23) and they were excluded in cases where their results were not “moderate” or “extremely severe”. Other measures used were Assessment of Quality of Life (AQoL)-8D (44), Positive and Negative Affect Schedule (PANAS) (24), 14-item Mediterranean diet scale and Simple Dietary Questionnaire (SDQ) (45). Other lifestyle and demographic factors were included in the study. For this study, participants would receive cooking workshops for 3 months and fish oil supplements for 6 months. In addition to the questionnaire assessment, blood samples and erythrocyte fatty acid analyses were done to measure the results. This study once again showed an improvement in mental

health when it came to following a MedDiet, as well as health in general. Blood samples showed that increased ω-3 PUFA eicosapentaenoic acid, ω-3 PUFA docosahexaenoic acid and decreased ω-6 PUFA arachidonic acid were associated with fewer depressive symptoms, less stress and improved overall health. One assumption why these results may have worked is the fact that free food was provided, such as olive oil and nuts which made the participants consume them more and proved that sometimes these nutrients would be consumed more if they were more easily accessible or cheaper.

Another study on 77 outpatients tried to see if there is a correlation between selenium, zinc, magnesium, vitamin B, iron, folate serum and serum selenium levels in one's body and MDD (46). Zinc, iron, and selenium are important micronutrients for development and growth (47). In this study, outpatients already diagnosed with MDD by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (48), over the age of 18, were randomly assigned either to the control group or to the active treatment group. The active treatment group received instructions about daily physical activity and dietary habits correlated with the MedDiet they should follow for the duration of the study. At the end of the study, the MINI (21), the Hamilton rating scale for depression (HAM-D) (25), the BDI (22), and the Clinical Global Impression scale (CGI) (26) were used to measure the participants' progress. Results showed no significant correlation between these micronutrients and MDD in either of the groups, except for a slight negative correlation when it came to serum selenium.

3.2. Studies focusing on depressive symptoms

The following studies did not require a formal diagnosis of MDD, but rather checked for depressive symptoms occurring over a shorter period of time.

A study was conducted on the population in Europe, over 50 years old. This study's aim was to measure the correlation between a MedDiet, lifestyle, cardio metabolic diseases, and depressive symptoms (49). Information about socio-demographics and health in general, indicating other lifestyle factors, was gathered from the SHARE – Survey of Health, Aging and Retirement in Europe (50). The factors this study connected were cardio metabolic disorders, body mass index (BMI) and mental health. For measures of depressive symptoms, the EURO-D scale (51), included in the SHARE questionnaire, was used with values set from 0 to 12, increasing numbers indicating increasing symptoms. Dietary patterns were assessed using a survey containing four questions asking about the frequency of consumption of products from a MedDiet. The results of the questionnaire were calculated into 1 (following a MedDiet) or 0 (not following the diet). When all results are considered, following a MedDiet is associated with a positive effect on mental health, and those elderly people who followed the diet were less likely to report depressive symptoms. In contrast to previous studies, this one had a larger cohort of elderly people from all around Europe, instead of focusing on one country alone, so the results can be considered more general and accurate when it comes to the whole population.

A study on a French population of 3523 adults with no diagnosed depression before the study, over the course of 13 years, was conducted to see if there is a protective effect of a MedDiet on depression (52). The Center for Epidemiological Studies Depression Scale (CES-D) (27), was used to assess depressive symptoms, and to determine the adherence to the MedDiet, a 24h diet report was taken and a relative MedDiet score (rMED) described by Buckland et al. (53) was calculated 6 days of the year, for 2 years so that all seasons and days of the week were considered. Higher adherence to the MedDiet was associated with older age, non-smokers, and higher educational level, but the protective effect

against depression was only significant in men, not when it came to women. For women, further research is needed.

A study on 3502 participants over the age of 65 in Chicago, Illinois, with no previous detection of depressive symptoms, looked for correlation between a MedDiet and depressive symptoms over time (54). A food frequency questionnaire and the MedDietScore (39) were used to assess adherence to a MedDiet, and the CES-D Scale (27) was used to determine depressive symptoms in participants. Other lifestyle factors were also considered. Higher intake of foods connected to a MedDiet showed a protective effect over time when it came to developing new depressive symptoms. Additional adjustments to the results to control for smoking, chronic diseases and alcohol use did not change the protective effect of the MedDiet against depression.

A study on 3062 primary care patients, 45 to 75 years old, was conducted to find correlation between their adherence to the MedDiet and depressive symptoms (55). The Patient Health Questionnaire (PHQ-9) (28) was used to assess their mental state, and MEDAS (42) was used to determine their dietary habits and adherence to a MedDiet. Those following a proper MedDiet had a lesser chance of developing depressive symptoms. This was also true for those who had other chronic diseases. More specifically, those who were female, younger, of higher BMI, eating more red meat, drinking sugary carbonated drinks, and not eating enough nuts, had a higher chance of developing depressive symptomatology.

A study on 2092 people over the age of 65 from a Greek population proved a better cognitive status and fewer depressive symptoms occur when practicing a MedDiet (56). A food frequency questionnaire and the MedDietScore (39) were used to assess adherence to a MedDiet, Mini-Mental State Examination (MMSE) (29) and GDS (16) were used to assess their mental state. Participants who had a higher adherence to a MedDiet were likely to be younger, female, of higher educational level, and lower

BMI. Adherence to a MedDiet was positively associated with cognitive well-being and negatively associated with depression.

A study on a Puerto Rican population of 1500 people aged 45-75 in the Boston area researched the correlation between an adherence to a MedDiet and depressive symptoms (57). The scale used to assess adherence to a MedDiet was the Trichopoulou scale (31). For self-assessment of depressive symptoms, the CES-D scale (27), containing questions about their mental state a week before the interview, was used. Higher scores on the scale indicated stronger depressive symptoms and a little less than 60% of participants scored enough to have significant depressive symptomatology. The scale was used again at checkpoints after 2 and 5 years. Other lifestyle factors were also questioned for the study. A cross-sectional analysis was used to determine the correlation between an adherence to a MedDiet and risk of depression with regard to other lifestyle factors, while a longitudinal analysis was used to determine solely the relationship between MedDiet and depression over the course of 10 years. All factors considered, higher adherence to a MedDiet was associated with lower CES-D scores at baseline, but the baseline adherence did not affect the results on the CES-D scale 5 years later. It appears depressive symptomatology was lower 5 years later in most participants, but not related to their scores on the Trichopoulou scale.

A study on 1018 elderly French people from three different cities, aged 65+, lasted over the course of 15 years and originally aimed to find a correlation between cardiovascular diseases and dementia (58). Adherence to a MedDiet was assessed by a questionnaire and using a MEDI-LITE score proposed by Sofi et al. (59), while the depressive symptoms were determined by an interview with a neuropsychologist using a CES-D scale (27). The results of the study did not show any significant correlation between a MedDiet and depressive symptoms over time. Only when the definition of MDD on the scale was restricted to more severe results, the correlation was shown with a slight protective effect of

a MedDiet against depressive symptoms. The symptoms were more closely associated with other factors such as gender, age, and marital status.

A study on 450+ elderly people aged 70 to 73 was conducted on a non-Mediterranean population from Scotland (60). The HADS scale (15) was used to self-assess depressive symptoms, and a 168-item food frequency questionnaire to assess adherence to a MedDiet or the Health Aware Diet (simply high fruit, low meat intake). The goal was to see if there is truly a correlation between a MedDiet and depression or is it the healthy diet in general lowering depressive symptoms. Their blood was also examined to check levels of serum CRP, fibrinogen levels, albumin, IL-6, transferrin, and ferritin. At the 3-year follow up, it was shown that the MedDiet influenced lower inflammation levels, but they were not correlated to depressive symptoms, while the Health Aware Diet did not have any impact on either depressive symptoms or inflammation levels.

Another study conducted on 388 elderly people aged 90-99 years in an Italian nursing home, investigated the correlation between a MedDiet and the risk of late-life depression (61). Food questionnaires and MedDietScore (39) were used to assess adherence to a MedDiet, and mental health examination and tests, as well as a shorter version of the GDS (16) were done to detect depressive symptoms. This time patients with higher adherence to a MedDiet had slightly lower chance of developing depressive symptoms, more significantly when it comes to women. By analysing specific food groups and difference in their intake between participants, it was determined that some food groups specific to a MedDiet, like cereal, fruit, and olive oil, had a protective effect on depressive symptoms. This led to a conclusion that some characteristics of a MedDiet have a protective effect against MDD. The difference between depressed and non-depressed participants was rather connected to their marital status, gender and walking ability.

4. Discussion

Table 2. A summary of all the studies concerning the effect of the MedDiet on MDD mentioned in the paper, in order of descending number of participants.

Study (reference)	Number of participants	Age	Demographic group	How was adherence to a MedDiet determined	How was depression defined	Were the results significant	Other factors considered
(49)	> 126,729	50+	European men and women.	A 4-question survey.	EURO-D scale.	Yes, protective effect.	Gender, age, marital status, ethnicity, education, employment, physical activity, smoking.
(30)	49,261	29-49	Swedish women.	Trichopoulou scale.	ICD (clinical diagnosis and/or SSRIs).	Yes, protective accumulative effect.	Age, body weight, height, education, smoking, diabetes mellitus, physical activity.
(32)	9,670	NEI.	Men and women.	Food frequency questionnaire (focus on B vitamins and ω-3 fatty acid rich foods).	Based on previous diagnosis and antidepressant use.	Yes, but selective and different in men and women.	Gender, age, marital status, employment, weight, height, smoking, caffeine and alcohol intake, physical activity, chronic diseases.
(35)	3,923	55-80	Spanish men and women.	14-item MedDiet adherence questionnaire.	Determined by a professional.	No.	Age, gender, BMI, smoking, educational level, marital status, alcohol intake, total energy intake, physical activity, chronic diseases.

(52)	3,523	NEI	French men and women.	rMED.	CES-D scale.	Yes, protective effect only in men.	Age, gender, education, physical activity, marital status, BMI, smoking, chronic diseases, energy intake, alcohol.
(54)	3,502	65+	Men and women from Chicago, Illinois.	MedDietScore.	CES-D scale.	Yes, inverse association.	Age, gender, race, education, yearly income, widowhood, calorie intake, BMI, smoking, alcohol consumption, medical conditions.
(36)	3,172	≈37	Iranian men and women.	Trichopoulou scale.	HADS, GHQ.	Yes, protective effect.	Age, gender, energy intake, marital status, education, smoking status, family size, home ownership, diabetes mellitus, use of anti-psychotic medications, dietary supplements.
(55)	3,062	45-75	Men and women.	MEDAS.	PHQ-9.	Yes, protective effect.	Gender, age, place of birth, marital status, work activity, educational level, BMI, weight.
(38)	2,718	65+	Mediterranean men and women.	MedDietScore.	GDS.	Yes, protective effect.	Gender, age, marital status, smoking, financial status, educational level, cholesterol, diabetes, coffee, alcohol, and tea intake.
(56)	2,092	65+	Greek men and women.	MedDietScore.	MMSE, GDS.	Yes, protective effect.	Age, gender, BMI, educational level.

(40)	1,634	18-65	Dutch men and women.	Division of MedDiet into 11 food groups.	CIDI, IDS, BAI, and FEAR.	Yes, protective effect, especially vegetables, fruit, and non-refined grains.	Gender, age, marital status, education, smoking, physical activity, daily energy intake.
(57)	1,500	47-75	Boston area Puerto Rican men and women.	Trichopoulou scale.	CES-D scale.	Yes, inverse association.	Gender, age, physical activity, BMI, chronic diseases, smoking, alcohol use, education, marital status.
(58)	1,018	65+	French men and women.	MeDi-Lite score.	CES-D scale.	Yes, but only when severe cases of MDD were considered.	Gender, age, marital status, education, living conditions, smoking, physical activity, total energy intake, BMI.
(60)	450+	70-73	Scottish men and women.	Food questionnaire and specific nutrient intake.	HADS.	Yes, MedDiet over Health Aware diet, but only in regard to inflammation levels.	Levels of serum CRP, fibrinogen, Albumin, IL-6, transferrin, ferritin.
(61)	388	90-99	Italian men and women.	MedDietScore.	GDS.	Yes, characteristics of a MedDiet protect from depression.	Age, gender, education, marital status, weight, BMI, smoking, drug use, chronic diseases.
(41)	273	≈51	NEI	MEDAS.	MINI, BDI-II.	Yes, but only at baseline.	BMI, metabolic syndrome.

(43)	152	18-65	Men and women.	14-item Mediterranean questionnaire and SDQ.	DASS-21, AQoL-8D, and PANAS.	Yes, inverse association.	Age, gender, education, income, marital status, sleeping habits.
(46)	77	18+	Men and women.	Participants followed the given guidelines.	DSM-IV, MINI, HAM-D, CGI.	Yes, but only serum selenium levels.	None.

Looking at all these studies, it seems there generally is a positive effect of the MedDiet on one's mental state in most of them (Table 2). The difference is how significant the results are and how strong the correlation is. What can be stated for sure is that none of the studies found a negative effect of this diet on depressive symptoms in a way that it would worsen them or cause them to occur. Moreover, the two largest studies, one gathering 12, and the other 5 times more participants then the next in line, showed the protective effect of a MedDiet. There are some potential caveats to consider when reviewing the results, and those will be discussed in this chapter.

When it comes to population, often the study was focused on a highly specific group of people, like citizens of the same country within the same age group, and many of them only focused on elderly people. This brings up a problem that there is no study conducted on a bigger population that would use the same methods on all participants and lead to more significant general results. Although, the fact that there are so many studies which altogether cover most areas of the world is helpful since looking at them all, we can try to conclude some general facts about the impact of this diet.

Almost all the studies relied on questionnaires to assess adherence to MedDiet, and some used questionnaires to self-assess depressive symptoms, which leads to the question of how trustworthy they truly are. Participants can easily lie in the questionnaires for various reasons, even accidentally because of false recollection, and that can affect the results greatly. The most reliable option when it comes to determining depressive symptoms of MDD would be a visit to a professional who could confirm their diagnosis. More studies need to be done focusing on the molecular background of the MedDiet and micronutrients in the organism to determine whether, and which of them exactly, have an impact on bettering mental health.

Another obstacle in determining the effect of the MedDiet is whether that is the real cause of the protective effect over development of depressive symptoms, or other healthy habits that, in many cases, came with it. Participants who followed the MedDiet during a longer course also, for example, tended to be more active, non-smokers, of higher educational level and married (30,49,58,61). All these factors are already well known to have a positive effect on mental health, so it is difficult to determine if the MedDiet was really the main protective measure against mental illness or if it was other factors that prevailed. Although, in one of the studies, smoking, partner status and physical activity were considered, and they did not change the success rate of the MedDiet on preventing depressive symptoms (40). One study also pointed out that during an early stage of MDD development, people tend to have unhealthier lifestyle habits (30). Studies can seem to show a correlation between unhealthier eating habits and depressive symptoms when the beginning of an MDD might be causing those habits. Some of the studies did not even consider other lifestyle factors, or only considered a few, and just focused on depressive symptoms and diet without connecting other reasons for their correlation, which can also cause a misinterpretation of results (46).

Nevertheless, since most studies concluded the positive effect of the diet, even when other lifestyle habits are taken into account, their effect should not be so strong as to lead to false conclusions in this many studies. Another reason for that is the fact that in the various studies, different lifestyle factors were considered, which means there is no specific factor such as marital status or smoking that might be connected to false results in all the studies combined. Furthermore, there is also a danger of publication bias, and people are more likely to publish thesis with positive results that confirmed their hypothesis.

In some cases, results depended on the definition of depression. One study used both a narrower and a broader definition of depression (30). When considering the narrower definition, results showed even higher

correlation between the MedDiet and depression. It showed an overall protective effect of the diet on mental health. This makes it easier to conclude that the MedDiet did in fact have a big impact on depressive symptoms since the effect was stronger when the depressive symptoms were more severe. Overall, there was a difference with studies that defined depression with just a self-assessment of depressive symptoms that occurred over a lifetime, or use of anti-depressants in the past, and studies that considered diagnosed MDD itself. This also makes it harder to look at the results in general, although another study, the second largest study by the number of participants, also found that the protective effect of MedDiet is stronger when a more serious case of MDD is considered (58). If more studies looking at severe cases and broader population should confirm this, then it will mean that the MedDiet definitely has a protective effect against MDD because the more severe the case, the stronger the correlation.

A study on 612 participants looked deeper into their gut microbiome to see if the Mediterranean diet changes it and if that is the reason for cognitive improvement (62). It was noticed that the starting point of microbiome was different when it came to populations from different countries. The results showed there was an increase in species previously linked with anti-inflammatory properties, and production of short chained fatty acids, while there was a decrease in species linked with type 2 diabetes. This suggests that a MedDiet alternates the microbiome to positively affect overall health. This is also a possible explanation of how it might affect, or protect from, MDD. Flavonoids are thought to decrease the risk of depression (63), and they are found in dark chocolate, red wine, berries, herbs, and tea, which are included in the MedDiet. Although it is not determined how they might affect the depressive symptoms exactly, they might be another reason why the MedDiet shows such a protective effect.

While some of the studies mentioned in this thesis did look at specific nutrients included in the MedDiet to see which exactly might be causing the improvement in mental health, they had limitations such as: the focus was only on a few of the nutrients contained in the MedDiet, the cohort size is rather small compared to other studies, and the results only guide us to potential future studies (46). They are a good starting point for future hypotheses and bigger studies concerning nutrients or the lack of which could be causing the progression of mental illnesses but are not yet enough to determine if nutrients such as B vitamins or ω-3 fatty acids have a significant effect on MDD (32).

5. Conclusion

Many studies managed to find a protective effect of the MedDiet against development of depressive symptoms, some even against a diagnosed MDD. The difference is the severity and duration of symptoms. Diagnosed MDD implies more severe symptoms over a long period of time. Research studies in this thesis included many different populations, different numbers of participants, different scales to determine depressive symptoms and different ways to calculate adherence to the MedDiet, but most of them gave similar results. Whether the study was conducted over a set period of time and looked at people's mental state before and after implementing the MedDiet, or it looked at the overall lifelong habits of people already practicing the MedDiet, it is clear that the majority of them gave the same outcome: the MedDiet is associated with better mental health and milder symptoms in MDD, even in severe cases. More studies on this topic would be helpful, especially those on a wider population of wider age range where the methods to determine MDD and adherence to the MedDiet would be the same for all participants, or those researching specific nutrients included in this diet to find a more specific reason for this correlation.

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