Mediterranean diet and its low-antigenic and anti-inflammatory properties on fibromyalgia: a systematic review

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ABSTRACT

Objective. *The Mediterranean diet is known for its antioxidant, anti-inflammatory, and low-antigen properties. The rationale is that this diet can modulate fibromyalgia (FM) symptoms for patients, but it has not been reviewed focusing on its low-antigen and anti-inflammatory properties. The objective of this review is to understand whether these properties of the Mediterranean diet can potentially alleviate symptoms of FM.*

Methods. *This study was conducted using the 2020 version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. Two electronic databases- PubMed and Google Scholar, were searched for interventional, observational, therapeutic, and clinical trial articles published between 2019 and 2024. Key search words included: 'Fibromyalgia' 'Mediterranean Diet' 'Low-Antigen Diet' 'Anti-inflammatory Diet' 'Omega3' and 'Vitamin D'.*

Results. *Of 88 records screened in the title/abstract stage, 5 interventional, 5 observational, 0 therapeutic, and 0 clinical trial articles were included in the systematic review. The sample sizes in interventional studies varied between 13 and 84 and for observational studies varied between 84 and 442. Evidence suggests that adherence to a Mediterranean diet is associated with significant improvements in FM-related symptoms, including chronic widespread pain, autonomic dysfunction, persistent fatigue, sleep disturbances, and cognitive impairments such as 'fibro fog'.*

Conclusion. *The articles studied within this review show that there is a relationship between the gut and how FM symptoms can be affected. They suggest that placing patients with early symptoms of FM on a Mediterranean diet may have a low to moderate effect on manifestation, especially before medications are introduced.*

Introduction

A healthy diet is essential to maintain good health and prevent non-communicable diseases. This paper focuses on anti-inflammatory and low-antigen food properties as they represent key elements in the Mediterranean diet and have been found to mediate disease symptoms.

Fibromyalgia

The focus of this review will be on fibromyalgia (FM), a disorder that is characterised by chronic widespread musculoskeletal pain and hypersensitivity to pressure. Other symptoms include fatigue, sleep and cognitive disturbances, and psychiatric symptoms. It is mainly seen as an increased response to a painful stimulus or pain following a stimulus that is not typically irritating (1). This disorder is often found concomitantly with autoimmune diseases, such as psoriatic arthritis and rheumatoid arthritis (2).

As autoimmune diseases affect women at higher rates, the same is true for FM. Women are six times more likely than men to be impacted by FM, primarily between the ages of 20–55 years old. The aetiology of FM is currently unknown as there are no physical abnormalities, and all lab work and radiographic tests of musculoskeletal structures are considered normal. Current ongoing studies hypothesise that FM may be due to a defect in pain regulatory mechanisms. This is a form of central sensitisation that amplifies neural

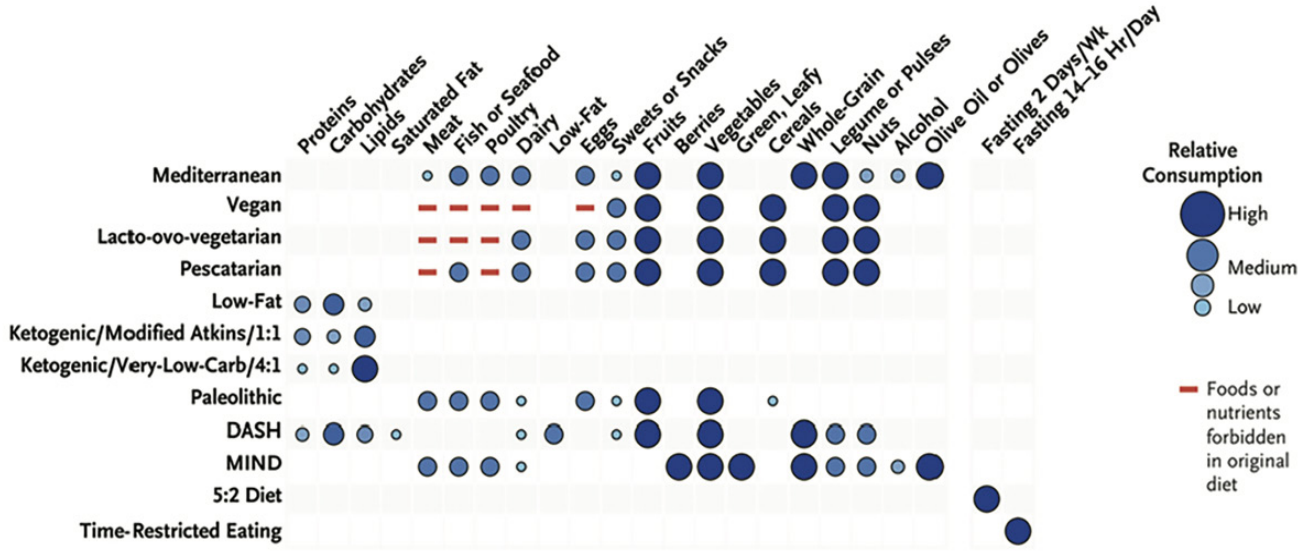

Fig. 1. Different diets and relative consumption of foods (8).

signalling within the brain and spinal cord, which leads to pain hypersensitivity.

FM is a disorder that is difficult to identify and can be easily missed during diagnosis by healthcare professionals. Due to this problem, it is difficult to understand exactly what the prevalence of the disorder is. Nonetheless, previous articles suggest that an estimated 2–3% (160–240 million people) of the world population is afflicted with FM. Within Italy, for example, 2% of the population has been diagnosed with FM, while in the United States, there is a 6.4% prevalence rate (3, 4). This differential may suggest a potential impact of diet on the likelihood of developing FM in populations that employ the Mediterranean diet compared to those that do not.

The classification criteria of FM are done according to the 2016 revision of the 2010/2011 ACR criteria (5).

Mediterranean diet

The Mediterranean diet is a long-standing nutritional approach in countries bordering the Mediterranean Sea, such as Greece, Italy, and Morocco. The diet is sourced and cultivated in each country, creating dietary differences based on geography and seasonal variability (6). Although they do slightly differ, they share common staples of olive oil, whole grains, fish, beans, leafy green vegetables, fruits, and nuts (*e.g.* walnuts, almonds, pistachios) (7). Additionally, moderate amounts of poultry, dairy products, and red grapes are consumed (7). It is in these staple foods within the diet that provide essential antioxidant and anti-inflammatory properties. While many other interesting diets are available for treating rheumatic diseases, we focused on the Mediterranean diet as it has considerable overlap with other diets used in medicine (8). Figure 1 highlights food consumption in different medicinal diets, highlighting the overlap between the Mediterranean diet and other medicinal diets such as the Palaeolithic and MIND diets.

Antioxidants

As cells in the human body turn food into energy, they inadvertently generate and release free radicals. These free radicals have the potential to damage cells and genetic material as they are unstable molecules in need of an electron. They can also cause oxidative stress, damaging cells and leading to chronic diseases (9). Consumption of food rich in antioxidants can help protect humans from damage caused by free radicals. Antioxidants are molecules that are capable of effectively neutralising free radicals within the body, thereby reducing its potential for damage.

The Mediterranean diet is singularly rich in antioxidants due to its high consumption of fruits, vegetables, virgin olive oil, tree nuts, whole foods, and moderate consumption of wine or red grapes. Virgin olive oil is rich in a multitude of antioxidants, which have been found to have a positive effect on cholesterol and gene expression (10). Acidic fruits, vegetables, and whole foods have an abundance of antioxidants from phytonutrients, a compound produced by plants, and have been shown to accept and stabilise free radicals (11). Red grapes specifically, have been found to have antioxidant properties with protective benefits (12). Sage, mint, thyme, chamomile, and anise teas also contain antioxidant properties (13). Additionally, tree nuts, beans, and seeds such as sesame, watermelon, garbanzo, almonds, pine nuts, cashews, Brazil nuts, hazelnuts, and especially walnuts, are rich in antioxidants (14-16).

Anti-inflammatory

Components of the Mediterranean diet, including olive oil, fish, nuts, seeds, teas, whole foods, fermented dairy products, fruits, and vegetables, have been shown to have anti-inflammatory properties. These foods contain omega-3 fatty acids and vitamin D, which will be discussed further in this section.

Omega 3

Olive oil, fish, and nuts are monounsaturated fats, a type of healthy fat high in essential omega-3 fatty acids. Omega-3 fatty acids exhibit anti-inflammatory properties, well-establishing itself as a

Table I. Adequate intakes for omega-3s (18).

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months*	.5 g	.5 g		
7-12 months*	.5 g	.5 g		
1-3 years**	.7 g	.7 g		
4-8 years**	.9 g	.9 g		
9-13 years**	1.2 g	1.0 g		
14-18 years**	1.6 g	1.1g	1.4 g	1.3 g
19-50 years**	1.6 g	1.1 g	1.4 g	1.3 g
51+ years **	1.6 g	1.1 g		

*As total omega-3s.
**As ALA.

Table II. Recommended dietary allowances for vitamin D (21).

Age	Male	Female	Pregnancy	Lactation
0-12 months*	10 mcg	10 mcg		
1-13 years	15 mcg	15mcg		
14-18 years	15 mcg	15 mcg	15 mcg	15 mcg
19-50 years	15 mcg	15 mcg	15 mcg	15 mcg
51-70 years	15 mcg	15 mcg		
>70 years	20 mcg	20 mcg		

*Adequate intake.

tool for the prevention and treatment of a multitude of diseases. The omega-3 fatty acids are able to modulate several inflammatory pathways, with the ability to inhibit pro-inflammatory proteins and increase the production of inflammation-resolving enzymes (17). Additionally, omega-3 fatty acids have been found to stabilise and protect neural tissues by maintaining cell membranes (17). The adequate intakes of omega-3s can be found in Table I.

When an individual does not meet the necessary consumption of omega-3 fatty acids, they can show signs of deficiency. Signs of deficiency can be physical, such as the skin becoming rough, scaly, and presenting dermatitis (18). There are also internal impacts as the plasma and tissue concentrations of omega-3 fatty acids within the body decrease (18).

Vitamin D

Vitamin D (which is a hormone) is vital for maintaining health. It promotes calcium promotion in the gut and maintains calcium concentrations for bone health (19, 20). In addition to this critical role, Vitamin D has also been found to reduce inflammation and modulate cell growth and immune function (21). One can obtain necessary Vitamin D through both sun exposure and the consumption of foods rich in Vitamin D, although dark skin pigmentation, which produces melanin-blocking UVB, may block Vitamin D synthesis, creating health disparities (22). Within the Mediterranean diet, fish such as sardines and anchovies are high in Vitamin D, as well as dairy products, nuts, and seeds. Recommended dietary allowances for Vitamin D intake can be found in Table II.

When an individual is deficient in Vitamin D, adults can experience osteomalacia, which is an abnormal mineralisation of the collagen matrix in the bone (19). Osteomalacia causes the bones to become weak, thin, and misshapen, increasing the risk of fractures. In addition, individuals with vitamin D deficiency can experience bone and muscle pain (19).

Low-antigen content diet

The low-antigen content diet avoids foods with high antigenic properties and promotes foods with anti-inflammatory properties. Foods that are high in macromolecular antigens, such as meats, dairy products, and eggs are restricted from the diet, because foods with antigenic properties are suggested to contribute to the pathogenesis of disease in individuals (23). Instead, the low-antigen diet promotes increased vegetables, fruits, whole grains, legumes, olive oil, and fish for its benefits and defence against chronic and allergic diseases (24). This diet of low consumption of animal products and high consumption of plant-based products is similar in content to the Mediterranean diet, which is composed largely of unprocessed ingredients. Slight modifications to the Mediterranean diet have successfully removed allergens such as gluten (25) and dairy (26), making it low-antigenic.

Methods

This study was conducted using the 2020 version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (27).

Data sources and data collection

A systematic search was conducted by two independent researchers (EM, SJ) in two electronic databases- PubMed and Google Scholar. These databases were searched for interventional, observational, therapeutic, and clinical trial articles published between 2018 and 2024. Key search words included: 'Fibromyalgia' 'Mediterranean Diet' 'Low-Antigen Diet' 'Anti-inflammatory Diet" 'Omega3' and 'Vitamin D'.

For the Mediterranean diet and FM article selection we used PubMed MeSH advanced search: (Diet, Mediterranean [Mesh]) AND Fibromyalgia [Mesh]. For the anti-inflammatory properties and fibromyalgia article selection we used PubMed MeSH advanced search: (Anti-Inflammatory Agents [Mesh]) AND Fibromyalgia [Mesh]. For the low-antigen properties and fibromyalgia article selection, low-antigen was not a MeSH term, so we could not utilise PubMed MESH advanced search.

Articles published between January 2019 and July 2024 were included. This timeframe was decided to ensure the most up-to-date knowledge and findings were utilised. Any disagreements as to whether a paper should be included were resolved by consensus by authors EM and SJ. The last search was conducted on 11 July 2024.

Study design and eligibility criteria

Eligibility criteria required study popu-

lations to be diagnosed with FM. Study designs included in the analysis were interventional, observational, therapeutic, and clinical trial designs. We excluded pilot studies, university thesis publications, and papers written in languages other than English. Pilot studies were excluded due to the presence of small sample sizes, therefore limiting its ability to report on possible errors. University thesis publications were avoided as there can be a variability in quality of work, depending on the institution, as well as a potential bias within the work. Work written in languages other than English had limited accessibility and may have different peer review standards, which would have impacted the strength of this review.

Data collection process

After completing the database searches, we carefully screened each article's titles for relevance. If the article passed the initial screening of relevance, we read the abstract to ensure that it is suitable for inclusion, then read the full article. When an article was included for synthesis, data was extracted and both EM and SJ confirmed accuracy. All data collection and processes were analysed manually.

Results

Of 88 records screened in the title/abstract stage, a total of 10 articles were used in the analysis. A breakdown of the screening process can be found in Figure 2 for Mediterranean diet and FM, Figure 3 for anti-inflammatory properties and FM, and Figure 4 for the low-antigen properties and FM.

Of the 10 articles, 5 interventional, 5 observational, 0 therapeutic, and 0 clinical trial articles were included in the systematic review. The sample sizes in the interventional studies varied between 13 and 84 participants and for observational studies varied between 84 and 442 participants. Data from the selected studies including the reference, study methods, number of participants, length of intervention, and findings can be found in Table III for the Mediterranean diet and FM, Table IV for anti-inflammatory properties and FM, and Table V for low-antigen properties and FM.

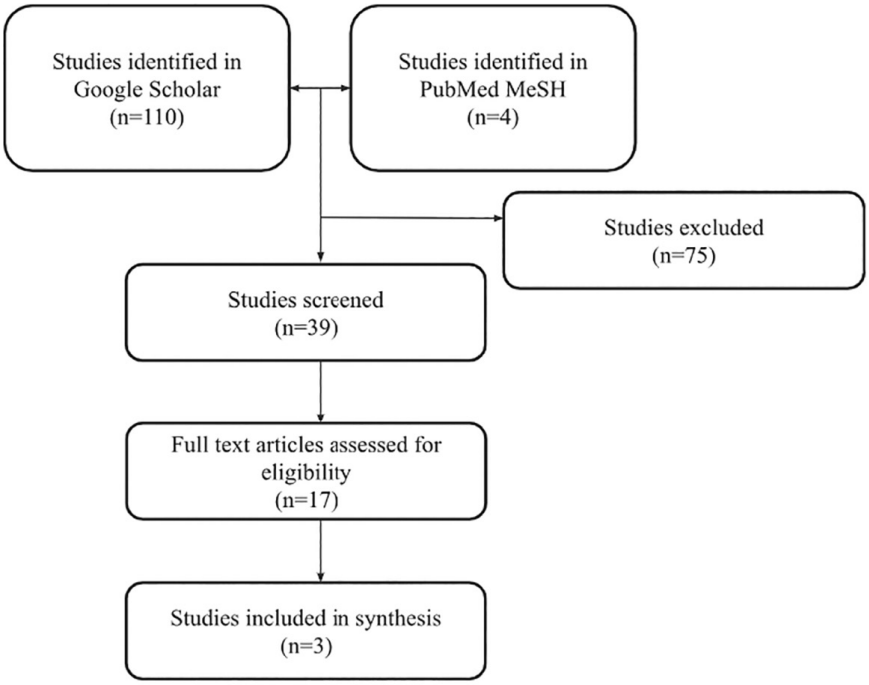

Fig. 2. Mediterranean diet and fibromyalgia article selection.

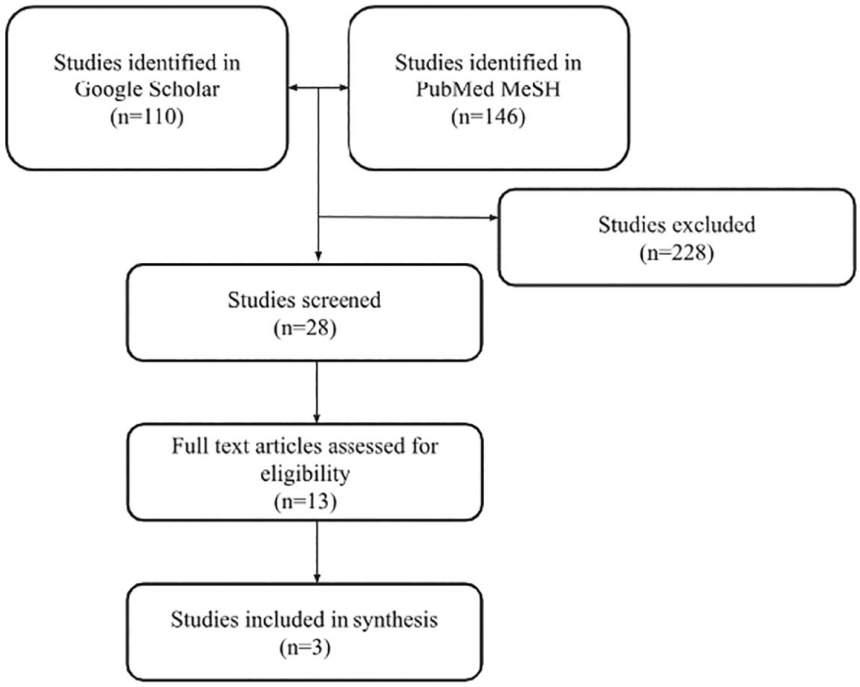

Fig. 3. Anti-inflammatory properties and fibromyalgia article selection.

Discussion

The studies above show the available research conducted to understand the relationship between the Mediterranean diet and its impact on the symptoms of FM. Especially when looking at specific aspects of the Mediterranean diet, such as anti-inflammatory and low-antigenic properties, there is evidence to support patients with FM using this diet, or modified versions of it, to ameliorate symptoms and improve quality of life.

Articles focusing on the effect of the Mediterranean diet and its effects on FM (Table III), found that the Mediterranean diet had a positive impact on disease manifestations such as pain inten-

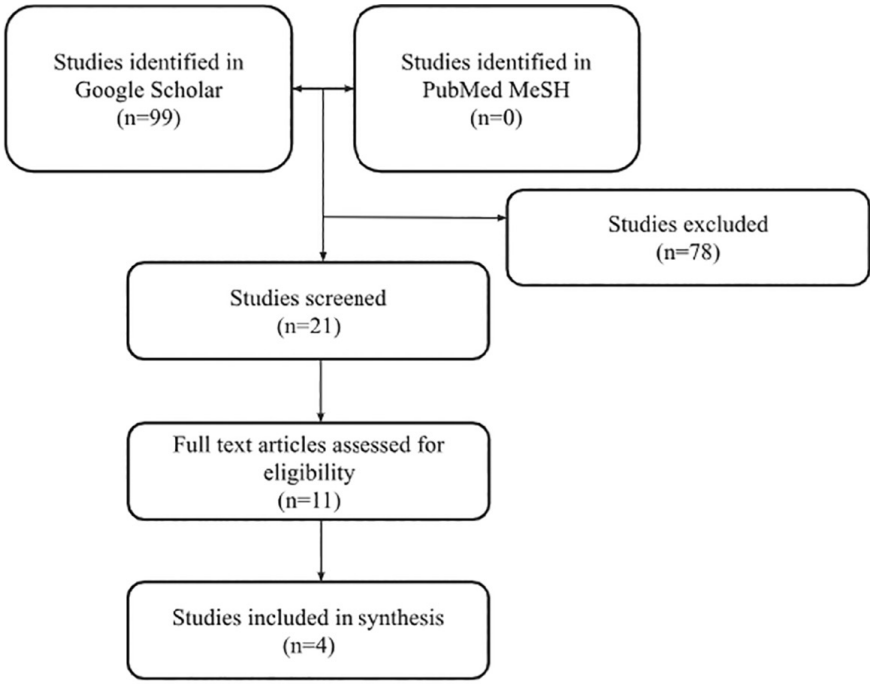

Fig. 4. Low-antigen properties and fibromyalgia article selection.

sity, fatigue, anxiety, and bone density. The experiment conducted by Casini *et al*. (29) compared participants placed on a personalised Mediterranean diet to those placed on a normal balanced diet. Results after 2 months showed that the outcome measures being assessed, anxiety, pain intensity, depression, fatigue, and quality of life, showed significant improvements.

Showcases articles that focus on general anti-inflammatory diets are presented in Table IV. These provide evidence that different aspects of FM-related symptoms can be targeted with dietary changes. Silva *et al*. found that switching to an anti-inflammatory diet showed a positive change in intervention group scores compared to the control group and that this diet was beneficial for patients regardless of demographic, disease duration, or body mass index.

Articles presented in Table V suggest a relationship between lowering the number of histamine-producing antigens in diet and reducing a variety of symptoms related to FM.

This may indicate that inflammation caused by food allergies can play a key role in the regulation of symptoms in immunological diseases. Gomez-Arguelles *et al*. (37) conducted a 6-month observational study on two groups of FM patients, one with an exclusion diet that removed any allergy-inducing foods while the other group continued with their current diets. After a couple of weeks on the exclusion diet, the intervention group was re-introduced to more vegetables and fruits. An additional study of interest is Martin *et al*. (35) which was a one-month antioxidant and anti-inflammatory diet treatment randomised-control trial of 13 women diagnosed with FM. This study found no significant improvement after one month of treatment, however, patients did report significant improvement in pain disturbance in work activities after that month. This highlights the need for longer-term studies as this study suggested symptom changes may take longer than originally planned.

The articles studied within this review show that there is a relationship between the gut and how FM symptoms can be affected. They suggest that placing patients with early symptoms of FM on a Mediterranean diet may have a low to moderate effect on manifestation, especially before medications are introduced (29).

To substantiate these clinical improvements observed in patients with FM following a Mediterranean diet, it is essential to explore underlying mechanisms, particularly the modulation of gut microbiota. The diet's high content of fibre, polyphenols, and healthy fats fos-

Table III. Summary of articles on the Mediterranean diet and fibromyalgia.

Reference	Study methods	Number of participants (n)	Length of studies	Findings
Proietti *et al*. (2024) (28)	Observational	186	1 online survey	Participants with better adherence to the Mediterranean diet had lower Fibromyalgia Impact Questionnaire (FIQR) scores and reported lower pain intensity.
Casini *et al*. (2024) (29)	Interventional	84	2 months	Intervention Mediterranean group showed significant reductions in brief pain inventory (BPI) scores, pain-related disability, impairment of motor activity, impairment of work activity, pain intensity, depression scores, anxiety scores, FIQ scores, multidimensional assessment of fatigue (MAF), and BMI. Both Widespread Pain Index (WPI) and Symptoms Severity (SS) showed improvement, but were not statistically significant.
Correa-Rodríguez *et al*. (2019) (30)	Observational	95	1 survey, 1 in-person visit to measure body composition	Adherence to a Mediterranean diet showed a significant association with bone ultrasound absorption.

Table IV. Summary of articles on the anti-inflammatory properties and fibromyalgia.

Reference	Study methods	Number of participants (n)	Length of studies	Findings
Correa-Rodriguez *et al*. (2020) (31)	Observational	193	1 structured survey, 1 face-to-face interview	Pro-inflammatory diets, according to Dietary Inflammatory Index, were found to be statistically significant in lowering Pressure Pain Thresholds for most tender point sites.
Silva *et al*. (2022) (32)	Interventional	46	3 months	Intervention group showed statistically significant improvement in Fibromyalgia severity scale FIQR, pain improvement in both Visual Analogue Scale (VAS) and BPI scales, gastrointestinal symptoms, sleep quality, fatigue, and quality of life. There was not a significant change in inflammatory biomarkers.
Rus *et al*. (2020) (33)	Interventional	30	3 weeks	The EVOO group experienced statistically significant reductions in red blood cell count, erythrocyte sedimentation rate (an inflammatory marker), and cortisol levels.
The ROO group experienced a statistically significant increase in mean platelet volume and cortisol levels. And experienced a statistically significant reduction in platelet distribution width, neutrophil-lymphocyte ratio, erythrocyte sedimentation rate, and fibrinogen.				

Table V. Summary of articles on the low-antigen properties and fibromyalgia.

Reference	Study methods	Number of participants (n)	Length of studies	Findings
Thomson *et al*. (2023) (34)	Observational	442	1 online self-reported questionnaire	Fibromyalgia was shown to be statistically significantly correlated with food-related symptoms such as food sensitivity, food allergy, and food intolerance.
Martin *et al*. (2019) (35)	Interventional	13	1 month	No significant improvement was made after one month of treatment. After one month, participants reported statistically significant improvement in pain disturbance in work activities.
Martin *et al*. (2019) (36)	Interventional	31	2 months	Olive-tree based nutraceuticals and a low-histamine diet (IGUBAC-diet) were used for 2 months in women with fibromyalgia. The supplement group experienced a statistically significant reduction in pain intensity, and symptom frequency, including: exhaustion, nausea, cramps, dry skin, zits, and itching. Significant changes in biochemical markers, albumin and globulin. Non-significant decrease in fatigue. The diet group experienced a statistically significant reduction in symptom frequency of exhaustion, acidity, reflux, cramps, tingling, and itching. Statistically significant improvement in biomarkers albumin, alpha, globulins, and beta globulins. There was a non-significant decrease in pain intensity and fatigue severity.
Gomez-Arguelles *et al*. (2022) (37)	Observational	84	6 months	With the use of histamine-release tests, aspects of the diet given to the treatment group did not include items that would result in a histamine reaction. The treatment group had statistically significant change in their Gastrointestinal Symptoms Rating Scale (with most reported improvement in bloating, belching, constipation, bowel sounds and hunger pain symptoms) and total body weight. Non-significant results were reported for FIQ and VAS.

ters a balanced gut microbiome, which may, in turn, attenuate systemic inflammation and lower pain sensitivity. Another potential mechanism of action is via oxidative stress reduction, due to the presence of antioxidants (*e.g*. olive oil, fruits, vegetables, and nuts) and may lead to decreased muscle fatigue and pain. Overall, all these mechanisms involve anti-inflammatory properties and as mentioned before, there is a chronic low-grade inflammation in FM and the Mediterranean diet may help mitigate this, resulting in lower pain levels and improved overall well-being (38).

Limitations of articles included

Length of intervention, sample size, and methods used are limitations of the articles included in this review. As nearly half of the studies were cross-sectional, with the longest study being 6 months, there is limited understanding of the long-term effects of the Mediterranean diet on FM symptoms. To better understand and create certainty in the Mediterranean diet mediation of symptoms for FM, there is a need for longer studies. Additionally, the sample sizes of the studies are too limited to be representative of the population. Having a larger sample size with a more diverse sample is imperative to ensure accurate average values and to be representative of the population demographics. Because of the small sample sizes, the studies included did not analyse individual factors such as race and ethnicity, which may be modera-

tors in the Mediterranean diet alleviation of symptoms.

An important limitation to consider is that there is diversity within the Mediterranean diet depending on which part of the Mediterranean one is located. The core principle of the Mediterranean diet across all countries is a high consumption of plant-based foods and olive oil, but within specific regions of the Mediterranean, a difference can be observed in the type of grains and spices that are used. For example, within the North African region (Morocco, Tunisia and Egypt), there is more consumption of couscous and bulgur as well as more prevalent uses of spices like cumin and coriander. Within the Western Mediterranean (France, Italy and Spain), they lean heavily on pasta, rice and cheese, while the Eastern Mediterranean regions (Greece, Turkey and Cyprus) rely on bulgur and yoghurt. Future studies need to further investigate the health outcomes, particularly in FM, associated with variations between regions in the Mediterranean diet and refine dietary guidelines accordingly (39).

Limitations of the review process

A limitation of this review was that it only accepted English-written articles. By accepting only English-written papers, we may have missed relevant publications.

Implications of the results for practice and future research

While generally there are low-inflammatory and low-antigenic properties in the Mediterranean diet, components of the diet may create a negative bodily response in some individuals. What causes inflammation for one, may not cause inflammation in another and may need further adaptations from other diets, such as gluten-free, FODMAP, and dairy-free diets. Because of this, there is a limitation within the studies included as the concept of low-antigen or low-inflammation needs to be revised and personalised in further studies.

The Mediterranean diet varies across regions therefore finding studies that use the exact same components was not possible and would not allow for a concise understanding of the impact of diet on disease outcomes. In addition to consistency between studies, it can be difficult for individuals to maintain a diet for a prolonged period of time. Future research would benefit from measuring diet consistency for analysis, to ensure diet is appropriately measured.

Further research needs to be conducted with larger sample sizes and longer time frames to understand the true effectiveness of the diet. As mentioned previously, many of the articles included in this review were observational, with few randomised control trials. Because of this, there is an opportunity for robust randomised control trials to establish clear causality between adherence to the Mediterranean diet and amelioration of the clinical symptoms of FM.

Another consideration for future studies is the gut-brain axis, as it has recently been a topic of discussion in how it relates to the presentation and progression of FM (40). Evidence increasingly suggests that gut microbiota may play a role in chronic pain, particularly in FM. The pathogenesis remains complex and multifactorial, nonetheless individuals with FM exhibit changes in the composition of their gut microbiota, characterised by an altered abundance of specific bacterial species. These microbial imbalances may influence the gut-brain axis modulating pain sensitivity and other clinical manifestations of FM. Overall, the gut microbiome represents a promising avenue for novel diagnostic and therapeutic strategies (41-42).

In review, the published evidence suggests that it is possible to alleviate FM symptoms, such as pain, fatigue, and brain fog, by changing to a Mediterranean diet with low-antigen and anti-inflammatory properties. Several studies have observed changes in patients with early to moderate stages of FM that were put on altered diets but, it is still necessary to further investigate the true impact of the Mediterranean diet as an early treatment option in FM.

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