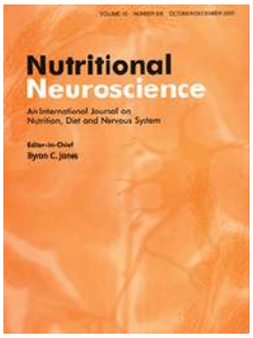

Taylor & Francis
Taylor & Francis Group

Nutritional Neuroscience

An International Journal on Nutrition, Diet and Nervous System

ISSN: 1028-415X (Print) 1476-8305 (Online) Journal homepage: https://www.tandfonline.com/loi/ynns20

Effect of omega-3 fatty acids and fish oil supplementation on multiple sclerosis: a systematic review

Welayah Ali AlAmmar, Fatima Hassan Albeesh, Layla Makki Ibrahim, Yasmin Yussuf Algindan, Lamya Zohair Yamani & Rabie Yousif Khattab

To cite this article: Welayah Ali AlAmmar, Fatima Hassan Albeesh, Layla Makki Ibrahim, Yasmin Yussuf Algindan, Lamya Zohair Yamani & Rabie Yousif Khattab (2019): Effect of omega-3 fatty acids and fish oil supplementation on multiple sclerosis: a systematic review, Nutritional Neuroscience, DOI: 10.1080/1028415X.2019.1659560

To link to this article: https://doi.org/10.1080/1028415X.2019.1659560

NUTRITIONAL NEUROSCIENCE
https://doi.org/10.1080/1028415X.2019.1659560

Taylor & Francis
Taylor & Francis Group

REVIEW

Effect of omega-3 fatty acids and fish oil supplementation on multiple sclerosis: a systematic review

Welayah Ali AlAmmar[a], Fatima Hassan Albeesh[a], Layla Makki Ibrahim[a], Yasmin Yussuf Algindan[a], Lamya Zohair Yamani[b] and Rabie Yousif Khattab [a]

[a]Clinical Nutrition Department, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia; [b]Department of Clinical Laboratory Sciences, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

ABSTRACT

Background: Multiple sclerosis (MS) is an autoimmune disease that affects the central nervous system, resulting in the degradation of the myelin sheath. Diet especially fish oils and omega-3 has been found to play an important role in MS. This work aimed to review the literature systematically for evidence on the effect of omega-3 fatty acids (EPA, DPA and DHA) on MS progression in adults.

Methods: The literature search was conducted in PubMed, Oxford, Cochrane, Embase, International pharmaceutical abstract, PsychINFO, and clinical trials government. The inclusions were studies performed on humans both male and female, aged 18 years at minimum, diagnosed with MS according to McDonald 2010 criteria. Otherwise, all studies were excluded.

Results: A total of 5554 studies were screened and seven were thoroughly focused on as they typically met the inclusion criteria. These studies showed the beneficial roles of fish oil supplementation and omega-3 fatty acids in improving the quality of life of MS patients. These roles were attributed to their beneficial effects on inflammatory markers, glutathione reductase, reducing the relapsing rate, and achieving balanced omega-6 to omega-3 ratios.

Conclusion: Omega-3 and fish oils supplementations have beneficial effects on reducing the relapsing rate, inflammatory markers, and improving the quality of life for MS patients.

KEYWORDS
Multiple sclerosis; diet; omega-3; fish oil; inflammation

List of abbreviations

Definition	Abbreviation
α-Linolenic Acid	ALA
Annualized Relapse Rate	ARR
Arachidonic acid	AA
Central Nervous System	CNS
Cerebrospinal Fluid	CSF
Cyclooxygenase-2	COX-2
Disseminated in Space	DIS
Disseminated in Time	DIT
Docosahexaenoic Acid	DHA
Docosapentaenoic Acid	DPA
Eicosapentaenoic Acid	EPA
Food Frequency Questionnaire	FFQ
Health-Related Quality of Life	HRQOL
Interferon Gamma	IFN-ϒ
Interleukin-1 Beta	IL-1β
Interleukin-10	Il-10
Interleukin-6	IL-6
Linoleic Acid	LA
Lipooxygenases	LOXs
Magnetic Resonance Imaging	MRI
Matrix Metalloproteinase	MMP-9
Multiple Sclerosis	MS
Not Available	N/A
Fatty Acids	FAs
Omega 6	n-6
Omega 3	n-3
Poly Unsaturated Fatty Acid	PUFA
Glutathione Reductase	GR
Primary Progressive Multiple Sclerosis	PPMS
Quality of Life	QOL
Relapsing Remitting Multiple Sclerosis	RRMS
Rheumatoid Arthritis	RA
Secondary Progressive Multiple Sclerosis	SPMS
Systemic Lupus Erythematosus	SLE
Tumor Necrosis Factor-Alpha	TNF-α

Introduction

Immune system defenses human body from foreign antigens that may cause infections and diseases. This protection manages and controls these foreign antigens by eliminating them in order to restore homeostasis [1]. If this protective mechanism is unable to distinguish between self and foreign antigens, the immune system might initiate an attack against its own cells and tissues leading to autoimmunity. Autoimmune diseases can be categorized into two types either being systemic or organ specific. There are many examples related to autoimmune disease as type 1 diabetes, rheumatoid arthritis (RA), celiac disease, systemic lupus erythematosus (SLE) and multiple sclerosis (MS) [2]. Multiple sclerosis (MS) is a chronic, neurological, inflammatory, and progressive

CONTACT Rabie Yousif Khattab rykhattab@iau.edu.sa, khattabry@gmail.com Clinical Nutrition Department, Imam Abdulrahman Bin Faisal University, Dammam 34212, Saudi Arabia

autoimmune disorder that typically affects the central nervous system of adults in their reproductive years causing major disabilities that can cause disorganize of the flow of information within the brain and between the brain and the body. It is considered the most common progressive neurologic disease of young adults worldwide [3,4]. According to the Atlas of MS, 2.3 million people were diagnosed with MS globally in 2013. The incidence may be higher as many people with MS remain undiagnosed in some regions [5]. The precise cause of MS remains unknown [6]. However, research has shown that there are risk factors that may increase the incidence of MS such as genetics and gender. Gender is a biological variable that plays a significant role in immune defense [7]. Men and women differ in their innate and adaptive immunological responses to foreign and self-antigens [8]. This can be explained by the hormonal changes during puberty, pregnancy, and menopause including estrogen, progesterone and prolactin in females and androgens in males. Females are at higher risk of developing MS than males [2]. MS ultimately affects the neurons. Neurons are surrounded by a fatty layer known as the myelin sheath. MS leads to demyelination which is a degradation of the myelin sheath and transection of neuron axons in patches throughout the brain and spinal cord resulting in axonal and neuronal death [9]. MS has different types including relapsing remitting multiple sclerosis (RRMS) which is the most common type of MS, the secondary progressive multiple sclerosis (SPMS) and the primary progressive multiple sclerosis (PPMS). Symptoms of MS vary from weakness of the limbs, dysfunction of organs such as bowel or bladder, mental changes, diplopia, and ataxia [6].

Risk factors that can contribute to neurodegenerative diseases have been described by the gut-brain axis hypothesis: stress, unbalanced diet, and drugs impact altering microbiota composition which contributes to dysbiosis [10,11]. Recent work underlines that diet can positively change microbiota composition and increase anti-inflammatory immune responses [12]. The promising effect of omega-3 supplementation in shifting gut microbiota balance towards an eubiosis status has been reported [13]. Studies showed that dietary habits have a predominant influence on the progression of MS [14]. Proper diet can improve the health and nutritional status of MS patients and control the disease or reduce its progression [15]. The effect of diet depends on the amount and type of food intake. Some nutrients have positive or negative effects. A healthy diet can help MS patients by positively affecting gut microbiota [16]. Whole grains and other high-fiber foods such as vegetables and fruits have protective effects and can delay the symptoms of MS and improve bowel movement [17,18]. Moreover, the consumption of low-fat dairy products containing high amounts of vitamin D and calcium decreases the risk of MS. Despite its high amount of heme iron that may help MS patients through regulating blood hemoglobin levels, red meat contains the omega-6 poly unsaturated fatty acid (n-6 PUFA) arachidonic which is the precursor of inflammatory eicosanoids that can negatively affect MS progression [14]. A Mediterranean diet, including unprocessed red meat, was associated with reduced risk of a first clinical diagnosis of central nervous system demyelination (FCD) in Australian adults. The addition of unprocessed red meat to a Mediterranean diet may be beneficial for those at high risk of MS [19]. PUFAs play a key role in the homeostasis of the immune system in which n-3 PUFAs have anti-inflammatory effect [20,21]. There is a lot of evidence that confirm the protective and beneficial effects of omega-3 FAs in inflammatory diseases including MS [22]. Figure 1 shows the pathway for producing eicosanoids of varied properties in the human body from the two types of fatty acids (n-6 and n-3) [23]. Both linoleic acid (LA) and α-linolenic acid (ALA) are considered the primary precursors for this pathway. The body is unable to convert n-6 into n-3 PUFAs and, therefore, the tissue levels of these fatty acids and their corresponding eicosanoid metabolites link directly to the amount of their dietary consumption [24].

Certain n-6 and n-3 PUFA metabolites have opposing physiological and pathological activities. Studies suggest that consuming more PUFAs, especially fish oil and n-3 PUFAs reduces the progression of MS. Increased dietary intake of n-3 PUFAs (mainly EPA and DHA) has been associated with a lower production of tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) and on the other hand, increased level of the anti-inflammatory cytokine interleukin-10 (il-10) [25–27]. In addition, consumption of omega-3 FAs was highly linked with improving quality of life (QOL) for MS patients [25]. Oils of certain plants and nuts, such as flaxseed oil are considered rich dietary sources for ALA, while fatty fish (e.g. salmon and mackerel) are rich dietary sources for EPA, DPA and DHA [20]. Sorto-Gomez et al. [28] reported the effectiveness of fish oil supplementation on increasing the glutathione reductase (GR) which is an important enzyme in MS status balance. Various studies suggest consuming more polyunsaturated fatty acid (PUFAs) especially fish oil and omega-3 fatty acids to reduce the progression of MS [25]. This systematic review was conducted to study the role of omega-3 fatty acids as a potentially preventive intervention against MS progression in adults. It was also aimed to investigate how much and which kind of these components would be protective against MS and to evaluate the quality of available evidence.

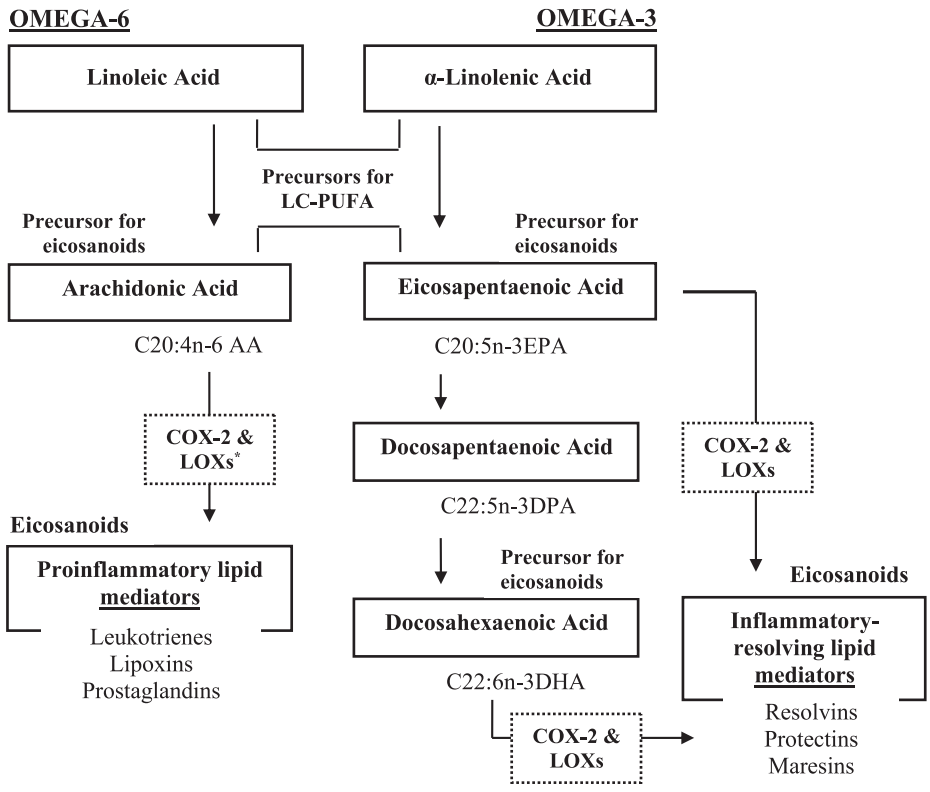

Figure 1. Role of n-6 and n-3 fatty acids in the production of eicosanoids in the human body. *COX-2 = cyclooxygenase-2; LOXs = lipooxygenases; AA = arachidonic acid; EPA = eicosapentaenoic acid; DPA = docosapentaenoic acid; DHA = docosahexaenoic acid. Adapted from Hidaka et al. [23].

Methodology

Literature search

Different reviewers independently searched the databases covering the literature from 2009 up to 2018. Search engines that were used included PubMed, Oxford, Cochrane, Embase, International pharmaceutical abstract, PsychINFO, and clinical trials government. Key words and specific terms used in the search along with the number of studies found are listed in (Table 1). Combination of these terms and filters regarding study design and type (ie, randomized controlled trial, cohort study, follow-up study, and controlled clinical trial) were used to obtain the search results.

Criteria for inclusion and validation of study sample

In order to provide a focused systematic review, inclusion and exclusion criteria were developed. Studies with longitudinal, prospective observational or interventional designs were considered. Studies included were those performed on humans both male and female aged 18 years or older, diagnosed with MS according to McDonald 2010 criteria [29] (Figure 2). These studies were all written in the English language. The excluded studies, however, were those involving MS patients having other issues as chronic diseases, pregnancy, lactation, physical or mental disabilities, patients with other autoimmune diseases, or any study that did not particularly represent the relationship between MS and omega-3 fatty acids.

In April 2001 an international panel recommended new diagnostic criteria for MS [30]. The McDonald criteria were revised in 2005 [31], in 2010 [29] and recently in 2017 [32]. Since this review was intended to cover the work published during the period from 2009 to 2018, the inclusion criteria of this systematic review were to include the studies conducted on adults aged 18 years and over who were diagnosed with MS according to McDonald 2010 criteria [29] as the latest published revision of McDonald criteria in the respective period. The last revision of McDonald criteria [32] was published only in 2018 after the included studies had been done and published. The McDonald Criteria incorporate clinical evaluation with magnetic resonance imaging (MRI) scans in establishing MS. Like an earlier approach, it also requires evidence of damage to the central nervous system (CNS; the brain, spinal cord and optic nerves) that is disseminated in time (occurs on different dates)

Table 1. Source of reviewed articles for potential inclusion in the current study.

Terms	PubMed	Oxford	Cochrane library	Embase	International pharmaceutical abstract	Psych INFO	Clinical Trials Gov	Total
Multiple sclerosis	2300	91	68	51	60	79	1766	4415
MS and diet	274	3	2	0	8	0	41	328
MS and nutrition	295	3	0	0	1	0	4	303
Dietary patterns and MS	10	0	0	0	0	0	0	10
MS and omega-3	10	0	2	0	0	0	2	14
MS and oils used	5	0	0	0	19	0	0	24
MS and fish oils	4	0	5	0	1	0	4	14
MS and PUFA	6	1	1	0	5	0	1	14
MS and linolenic A	4	0	2	0	0	0	0	6
MS and EPA	1	1	0	0	0	0	1	3
MS and DHA	7	1	0	0	0	0	1	9
T cell and MS	297	6	0	0	43	0	10	356
T cell and omega-3	28	0	6	0	23	0	1	58
Total	3241	106	86	51	160	79	1831	5554

and space (found on two or more parts of the CNS). The 2010 revision of McDonald criteria [29] reflected the need to simplify whether myelin damage seen on an MRI according to DIS and/or DIT was distinctive of MS. The revision also improved the criteria's applicability to other populations (pediatric, Asian and Latin Americans), since it was developed using a white and Western patient population. The last revision of McDonald criteria was done in 2017 [32] when the International Panel on Diagnosis of Multiple Sclerosis reviewed the 2010 McDonald criteria and introduced some updates. They stated that the presence of CSF-specific oligoclonal bands allows a diagnosis of multiple sclerosis in patients with a typical clinically isolated syndrome and clinical or MRI demonstration of dissemination in space. Furthermore, symptomatic lesions may be used to prove dissemination in space or time in patients with supratentorial, infratentorial, or spinal cord

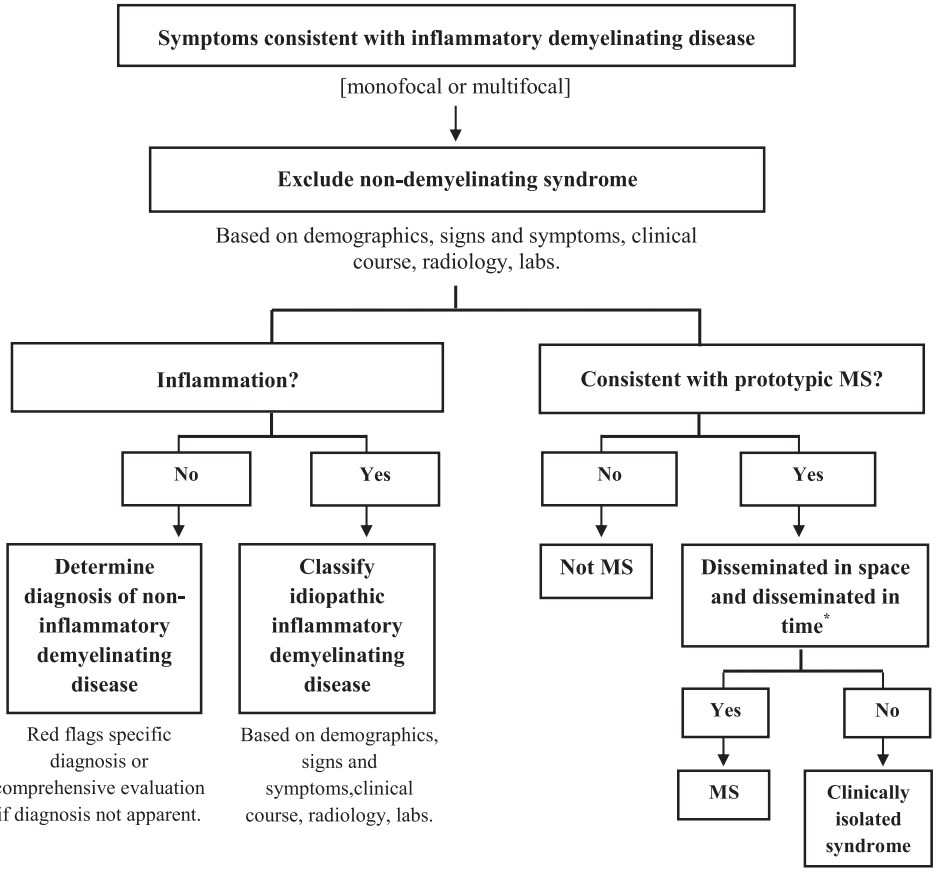

Figure 2. Guidelines for MS diagnosis: 2010 McDonald Criteria [29].

syndrome. The cortical lesions can be further used to demonstrate dissemination in space.

Study selection

The total articles retrieved were 5554 (3241 from PubMed, 106 from Oxford, 86 from Cochrane, 51 from Embase, 160 from international pharmaceutical abstract, 79 from psych INFO, and 1831 from clinical trial) (Table 1). The primary selection was made by reading the title or abstract. The articles were then thoroughly screened as per detailed criteria where the most appropriate ones ($n = 7$) have been selected and the rest were excluded ($n = 5547$). The study selection process is described in Figure 3.

Systematic evaluation

The included studies were assessed for design, setting, and study population. The definition of MS was evaluated systematically according to McDonald 2010 criteria [29] taking into account assessment methods, assessment period, and intensity. Adequate diagnostic evaluation and the use of appropriate diagnostic criteria were checked from each study. To assess the quality of reviewed studies, an applicable measure was adopted based on the validated methods of Shamliyan et al. [33,34] and the Cochrane collaboration's tool for assessing risk of bias in randomized trials [35] according to the research aims of this review. This measure assessed the evidence in three domains of bias including the population representativeness, valid outcome assessment, and participants' drop-out or attrition. Good population representatives were those aged ≥18 years who have been diagnosed with MS according to McDonald 2010 criteria [29]. There were no specifically defined cutoffs for sample sizes, but a general rule was to have a sample size large enough to detect a clinically significant difference of 5% in event rates or an odds ratio or risk ratio increase of ≥1.5. Moreover, cohort studies typically require larger sample sizes to have the same power as a case–control study [36]. The limitations for age were defined because the prevalence of MS is high in young adults who tend to have their first symptoms between the ages of 20 and 40 [3,4]. The good or valid outcome assessment considered the definition of MS according to McDonald 2010 criteria [29]. Whenever reported in the study under selection, good attrition rate was defined as <20% loss or no response of participants. Thirty percent drop-out over a period of 5 years was considered as poor attrition rate, while 60% attrition rate over 20 years was not much [37,38]. The quality of evidence of the included studies was assessed based on the categories described earlier. Quality of evidence was defined as 'good' or low risk of bias if the study was rated as 'good' in the three domains.

Results

The main analyzed studies in this review ($n = 7$) [25,26,28,39–42] included a total of 240,914 subjects from both genders. Based on the population representativeness, outcome assessments, and attrition rate, the overall quality of evidence was good for these seven studies. They all included participants in the intended age group (≥ 18 years) with valid outcome assessments based on McDonald 2010 criteria [29] for MS diagnosis. In addition to the inclusion criteria described in the 'Methods' section, the quality of these studies has been further assessed scientifically by assessing the risk of bias as well as the overall strength taking the study purpose, design, outcomes, statistical analysis, limitation reporting, bias reporting and providing appropriate conclusion into account (Table 2) and technically (Table 3). The study was considered 'good' if it scored an overall quality of ≥75%. The seven selected studies scored good quality in different aspects. All of them had a clear purpose and research question, an extensive literature review and a proper conclusion. The results were statistically analyzed in five studies and the limitations and bias were reported in six studies. All the studies reviewed referred to omga-3 fatty acids and their effects on MS, relapses, symptoms, and disability progression time (Table 4).

Discussion

In cohort study conducted on 2303 participants (1896 females and 407 males), Jelinek et al [25]. investigated the effect of fish consummation and omega-3 supplementation on the quality of Life of MS patients using the MS quality of Life-54, diet habits questionnaire and dietary assessment tools. Patients who consumed fish three or more times weekly or those taking high doses of omega-3 FAs have lower levels of disability and are almost living with normal mobility ($\rho < 0.001$). In addition, the health-related quality of life (HRQOL) was better and showed a stronger association for those using omega-3 supplements of 1–20 ml/d or consuming fish more frequently. In contrast, the relapsing rate was not improved by consumption of fish or taking the supplements, but there was little improvement among patients who consumed both fish and flaxseed oils ($\rho < 0.005$). Similar to relapsing rate, both fish and flaxseed oils increased the stability of the disease. The study had some limitations from which self-reporting of the data

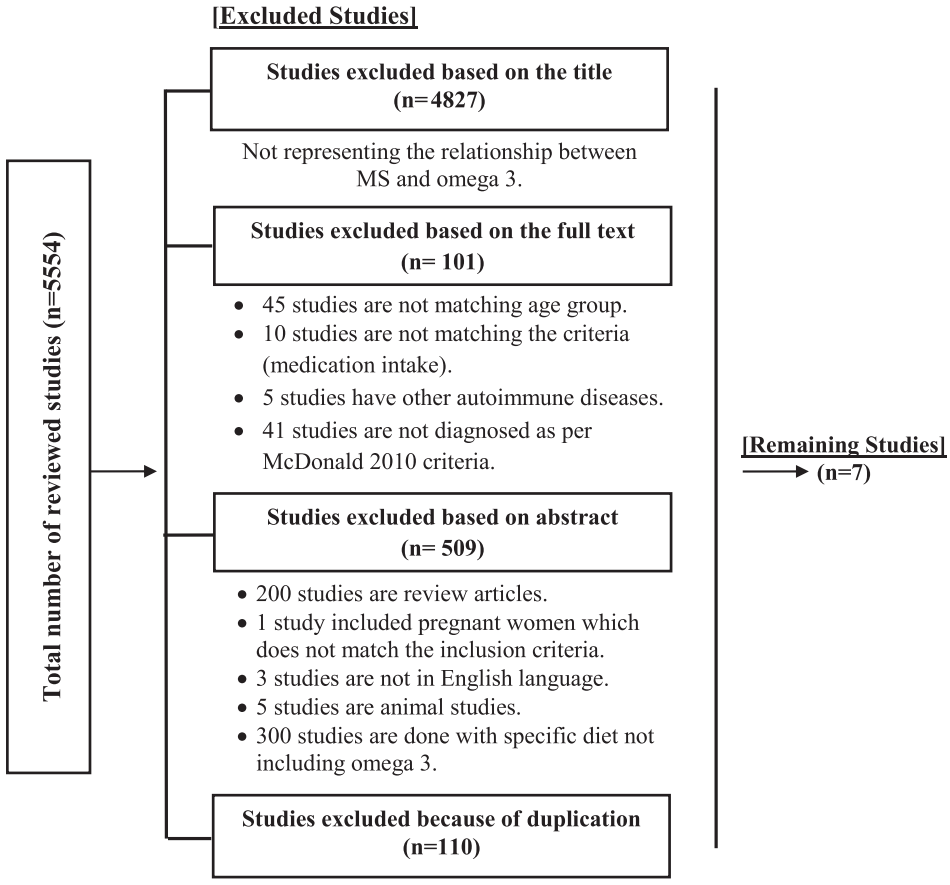

Figure 3. Screening of articles for potential inclusion in the present review.

was an important factor limiting the possibility to verify the reported data or to provide recommendation regarding the dose of fish, omega-3 or flaxseed oil. On the other hand, Wergeland et al. [43] found no difference in relapsing rate as well as on fatigue and QOL score between the group who consumed omega-3 and the placebo group. In

Table 2. Quality assessment of the studies included in the current review.

Quality Assessments	Pantzaris et al. [40]	Jelinek et al. [25]	Shinto et al. [39]	Bjørnevik et al. [41]	Zandi-Esfahan et al. [42]	Ramirez-Ramirez et al. [26]	Sorto-Gomez et al. [28]
1- Study purpose	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
2- Literature review	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
3- Clear design	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
4- Sample (described)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	No (0)	No (0)
5- Outcomes (reliable)	No (0)	Yes (1)	No (0)	No (0)	Yes (1)	Yes (1)	Yes (1)
6- Outcomes (validated)	Yes (1)	No (0)	Yes (1)	No (0)	No (0)	No (0)	No (0)
7- Prediction equation described	Yes (1)	Yes (1)	Yes (1)	No (0)	No (0)	Yes (1)	Yes (1)
8- Results statistically analyzed	Yes (1)	Yes (1)	Yes (1)	No (1)	Yes (1)	Yes (1)	No (1)
9- Limitation and bias reported	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
10- Appropriate conclusion	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
Overall quality (out of 13)	9 (90%)	9 (90%)	8 (80%)	8 (80%)	8 (80%)	8 (80%)	8 (80%)

Yes = 1, No = 0, N/A = 0.5.

Table 3. Technical assessment of the studies included in the current review.

Technical Assessments	Pantzaris et al. [40]	Jelinek et al. [25]	Shinto et al. [39]	Bjørnevik et al. [41]	Zandi-Esfahan et al. [42]	Ramirez-Ramirez et al. [26]	Sorto-Gomez et al. [28]
1- Was the spectrum of participant's representative of the patients who will receive the test in practice?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
2- Were selection criteria clearly described?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
3- Was the reference standard likely to classify the target condition correctly?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
4- Was the period between performing the reference standard and the index test short enough so that the target condition did not change between the two tests?	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
5- Was the selection of the sample verified using the reference standard?	Yes (1)	Yes (1)	Yes (1)	N/A (0.5)	Yes (1)	Yes (1)	Yes (1)
6- Did participants receive the same reference standard regardless of the index test result?	No (0)	Yes (1)	Yes (1)	Yes (1)	No (0)	No (0)	No (0)
7- Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	N/A (0.5)	Yes (1)	Yes (1)
8- Was the execution of the index test described in sufficient detail to permit its replication?	Yes (1)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)
9- Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
10-Were the index test results interpreted without knowledge of the results of the reference standard?	N/A (0.5)	N/A (0.5)	N/A (0.5)	N/A (0.5)	N/A (0.5)	Yes (1)	N/A (0.5)
11- Were the reference standard results interpreted without knowledge of the results of the reference standard?	N/A (0.5)	N/A (0.5)	N/A (0.5)	N/A (0.5)	N/A (0.5)	Yes (1)	N/A (0.5)
12- Were the same clinical data avilable when the test results were interpreted as would be avilable when the test is used in practice?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
13- Were un-interpertable, indeterminate, or intermediat test results reported?	N/A (0.5)	Yes (1)	Yes (1)	Yes (1)	N/A (0.5)	Yes (1)	Yes (1)
14- Were withdrawals from the study explained?	Yes (1)	N/A (0.5)	N/A (0.5)	N/A (0.5)	Yes (1)	Yes (1)	Yes (1)
Overall technical quality (out of 14)	10.5 (75%)	12.5 (89%)	12.5 (89%)	11 (79%)	11 (79%)	13 (93%)	12 (86%)

Yes = 1, No = 0, N/A = 0.5.

a study on 175,431 females from Nurses' Health Studies (1984–2004 and 1991–2009) women reported on diet using a validated FFQ every 4 years and 479 incident MS cases were identified during follow-up [41]. It was found that higher intake of total PUFAs at baseline was associated with a lower risk of MS ($\rho < 0.001$). Among PUFAs, only α-linolenic acid (ALA) was inversely associated with MS risk, however both EPA and DHA were not associated with MS risk. ALA may contribute to the immune pathway which controls the pathogenesis of MS by decreasing the inflammation markers. EPA and DHA, however, may have a role in decreasing the *Matrix Metalloproteinase (MMP-9)* levels in both the control and MS patients' groups ($\rho < 0.001$). This protein is one of the dangerous markers for immune cell migration. It is responsible for migration of immune cells towards the central nervous system by inducing the disruption of the blood brain barrier, so when it increases, the brain barrier will degrade.

In line with the preceding results, Shinto et al. [39] conducted a study on 10 participants who received 9.6 g/d of fish oil to determine the effect of fish oil and omega 3 on MMP-9 and Quality of life (QOL). The results showed that omega-3 FAs decreased the immune cell secretion of MMP-9 by 58% after 3 months of supplementation significantly ($p < 0.01$), and no improvement or deference in the QOL. Moreover, this effect was coupled with a significant increase in omega-3 FAs levels in red blood cell membranes. These results are in accordance with Riccio and Rossano [14] who reported that fish oil supplementation have a beneficial effect in inhibiting the expression of MMP-9, and that omega-3 supplementation can reduce the MMP-9 level in MS patients. In another study by Cunnane et al. [44] through the intervention with LCFA, the omega-3 FAs were reduced in plasma from MS patients and LA was reduced in erythrocyte ghosts from MS patients ($p < 0.0\ 1$).

A randomized double-blind placebo control study with 80 subjects [40] showed the effect of a novel oral nutraceutical formula of 1:1 omega-3 (DHA and EPA 3:1) and omega-6 (linoleic acid and γ-linolenic acid 2:1) fatty acids (PLP10) in relapsing remitting multiple sclerosis. The treatment significantly reduced the annualized relapse rate (ARR) and the risk of sustained

Table 4. Comparing the main studies investigated in the current review.

Reference	Country	Type of MS	Assessment	Dose of supplementation (if applicable)	Study duration	Participants F	M	total	Age Range (Y)	Outcome	Study type & Statistical test applied	Main result
Pantzaris et al. [40]	N/A	RRMS	Supplements of omega-3 (EPA.DHA, LA), vitamin E, and A.	Daily: 1650 mg EPA 4650 mg DHA 2000mg GLA 3850 mg LA 600 mg Other n-3 FAs 0.6 mg Vitamin A 22 mg Vitamin E	30 M	80	–	–	18–65 Y	Effect of fish oil supplement and vitamin PLP10 on QOF	Randomized double-blind, placebo-controlled, clinical trial rank test, Kruskal-Wallis rank test and Fisher's exact test	PLP10 reduce annualized relapse rate and disability with $p = 0.006$
Jelinek et al. [25]	US, UK, Austria and others	N/A	Used MS Quality of Life-54 (MSQOL-54)-52, EDSS, diet habits Questionnaire and dietary assessment tools with 22 items, assessed the average fish consummation weekly and omega-3 supplementation.	• 1–10 g/d • More than 11 g /d of fish oil or flaxseed oil or both or unspecified	12 M	1896	407	2303	18 and over	Effect the quality of life, disease activity and disability	Cohort study ANOVA, Fisher's exact test, and chi square test	Consummation of fish for more than 3 time a week can increase the quality of life, physical health and mental health ($p < 0.001$), take 1–20 ml /d of omega-3 lead to improve health related quality of life ($p < 0.001$)
Shinto et al. [39]	USA	RRMS	Omega-3 fatty acid (fish oil) supplementation and measuring: 1. Matrix metalloproteinase-9(MMP-9), 2. Peripheral blood mononuclear cell (PBMC) and 3. Red blood cell (RBC), and assess MS Quality of life inventory (MSQLI).	9.6 g/d of fish oil	6 M	–	–	10	18–65 Y	Effect the Matrix Metalloproteinase-9	Intervention	Omega-3 FA significantly decreased MMP-9 ($p < 0.01$)
Bjørnevik et al. [41]	N/A	N/A	Food frequency questionnaire and questionnaire on medical history and health related behavior.	–	1980–2007	238,371	–	–	25–50 Y	PUFA intake and risk of MS	Nurse health study Tow tailed	High intake of PUFA reduce MS risk ($p = 0.001$)
Zandi-Esfahan et al. [42]	Iran	RRMS	Fish oil supplementation Assess the EDSS and level of TNF-α, IL-Iβ, IFN-ϒ and IL-6.	1 g/d	12 M	–	–	50	18–45 Y	Effect of fish oil and inflammatory markers	Case control study t-test and Mann-Whitney U test, Chi-squared test and sample t-test or Wilcoxon signed rank test	Consummation of fish oil supplementation have no potential effect in lowering the serum levels of TNF-α, IL1β, IL6, and IFN-γ ($p > 0.05$) and the change of EDSS level ($p = 0.08$)
Ramirez-Ramirez et al. [26]	Mexico	RRMS	Fish oil supplementation. Assess the EDSS and level of TNF-α, IL-Iβ, il-6, nitric oxide catabolites, lipoperoxide and number of relapses.	4 g/d of fish oil	12 M	–	–	50	18–55 Y	Effect of fish oil and inflammatory markers	Case control study, use ANOVA and Mann-Whitney U test.	Fish oil have potential effect in lower the serum levels of TNF-α, IL1β, IL6 and nitric oxide ($P < 0.001$)
Sorto-Gomez et al. [28]	Mexico	RRMS	Fish oil supplementation. Assess the level of glutathione reductase and GSH/ GSSG ratio, lipid profile.	4 g/d of fish oil	12 M	–	–	50	18–55 Y	Effect of fish oil on fatty acid profile	Case control study Mann-Whitney U test	fish oil supplementation, increase the level of EPA and DHA and reduce AA and ratio of n-6/n-3, AA/ EPA

disability progression without any reported serious adverse events. The authors reported a shortage in the sample size because of the patients who dropped out from their project. Ramirez-Ramirez et al. [26] found that fish oil containing high amount of omega-3 PUFAs EPA and DHA had anti-inflammatory, antioxidant and neurologic effect. A daily supplement of 4 grams of fish oil had a significant effect in reduction the level of tumor necrosis factor alpha (TNF-α) ($\rho < 0.001$) which acts to increase the inflammation in the human body. It also reduces the level of Interleukin 1 beta (IL1β) part of cytokine which is a mediator of the inflammatory response Interleukin 6 (IL6) that stimulates the inflammatory and auto-immune processes and Interferon gamma (IFN-γ). The sample size, however, was not large enough to ensure the results and the outcome about the relapses duration and the duration itself between each relapse. These results are in line with Sedaghat et al. [18] who stated that diet low in omega-3 polyunsaturated fats and high in animal fats or saturated fats may increase the risk of MS.

Controversial results were reported by Zandi-Esfahan et al. [42] in a double-blind randomized placebo-controlled trial carried out with 74 participants who took 1g/day of fish oil as a dietary supplement. Administration of fish oil did not reduce the serum levels of TNF-α, IL1β, IL6, and IFN-γ compared to placebo. Similarly, it did not improve the disability in patients. Similar results were reported by Wergeland et al. [43] who determined the effect of PUFAs by randomized controlled trials and found no evidence of PUFAs as beneficial in relapsing rate and state of MS disease. Moreover, Sorto-Gomez et al. [28] conducted a study on 50 of MS patients who received 4 g/d of fish oil for one year. The results showed a significant change in glutathione reductase activity in fish oil group after 12 months of intervention ($\rho < 0.0001$), while the placebo groups had no changes during the study period. These results suggest the positive effect of fish oil on the antioxidant defense mechanisms of the cell. This effect is attributed to the immune-modulatory and antioxidant actions of n-3 PUFAs in reducing the production of pro-inflammatory mediators and increasing the production of anti-inflammatory mediators. Omega-3 FAs supplementation can decrease the level of pro-inflammatory eicosanoid formation leading to decrease the free radical which can improve the MS patient's health and decrease the relapsing rates [14]. The limited number of cases, the shortage in the study duration, and the inclusion of tocopherols in the placebo capsules given to the control group are the limitations that may confounded the outcome of the results as reported by the authors.

Strengths, limitations and recommendations of the study

This review summarizes the relationship between the supplementation of omega-3 fatty acids and MS. It handles a number of studies with large sample size to evaluate the relationship. On the other hand, the study has some limitations. It is not easy to find updated, clear and straightforward evidence and articles regarding the relationship between multiple sclerosis and omega-3 fatty acids. In most of the studies reviewed, the sample size taken in predominating studies was insufficient which may affect the finding. The duration of the intervention was usually not enough to evaluate the effect of fish oils or omega-3 supplementation on MS status. There is no systematic review on the link between fish oil and omega-3 supplementation with MS done before. Because of the lack of recent studies, further research is needed in this regard.

Conclusion

Omega-3 fatty acids and fish oil supplementation have many beneficial effects regarding to MS patients specifically and human body in general. Consumption of omega-3 fatty acids and fish oils supplementation can affect the level of inflammatory markers such as: TNF-A, IL-Iβ, IFN-ϒ And IL-6, relapsing rate, quality of life and the progression of MS disease as seen in the recent reviewed studies. The studies showed that 4 gm of daily omega-3 supplementation or fish oil is recommended. However, the effectiveness of this dose or supplementation varies depending on many factors especially the progression and disease status before starting the supplementation. Further studies are needed to determine the effectiveness of omega-3 fatty acids on MS health status.

Disclosure statement

No potential conflict of interest was reported by the authors.

Notes on contributors

Ms. Welayah Ali AlAmmar is a B.Sc. Graduate from the Clinical Nutrition Department at Imam Abdulrahman University, Dammam, Saudi Arabia.

Ms. Fatima Hassan Albeesh is a B.Sc. Graduate from the Clinical Nutrition Department at Imam Abdulrahman University, Dammam, Saudi Arabia.

Ms. Layla Makki Ibrahim is a B.Sc. Graduate from the Clinical Nutrition Department at Imam Abdulrahman University, Dammam, Saudi Arabia.

Dr. Yasmin Yussuf Algindan got her bachelor's degree from the King Faisal university in Dammam, Saudi Arabia in 1996. She obtained her masters and Ph.D. degrees in 2007 and 2016 from University of Manitoba, Canada and University of Glasgow, UK, respectively. She is currently working as assistant professor and chairperson for the Clinical Nutrition Department at Imam Abdulrahman University, Dammam, Saudi Arabia.

Dr. Lamya Zohair Yamani is an assistant professor at the department of Clinical Laboratory Sciences, Imam Abdulrahman University, Dammam, Saudi Arabia.

Dr. Rabie Yousif Khattab obtained his Ph.D. degree in Food Chemistry from Alexandria University, Egypt in 2004. From 2007 to 2010 he worked as a post-doctoral research fellow in the Department of Food and Human Nutritional Sciences at the University of Manitoba, Canada. He joined the Department of Process Engineering and Applied Science at Dalhousie University, Canada as a research associate in 2014. Dr. Khattab is currently working as associate professor at the department of Clinical Nutrition at Imam Abdulrahman University, Dammam, Saudi Arabia.

ORCID

Rabie Yousif Khattab http://orcid.org/0000-0002-1715-970X

References

[1] Wikiversity. Role of the immune system – [online] [cited 2019 July 16]. Available from: https://en.wikiversity.org/wiki/Role_of_the_immune_system 2019.
[2] Ngo S, Steyn F, McCombe P. Gender differences in autoimmune disease. Front Neuroendocrinol. 2014;35(3):347–69.
[3] Evans C, Beland SG, Kulaga S. Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. Neuroepidemiology. 2013;40(3):195–210.
[4] GBD Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the global burden of disease study 2015. Lancet Neurol. 2017;16(11):877–97.
[5] Multiple Sclerosis International Federation. Atlas of MS 2013; mapping multiple sclerosis around the world 2013; Available from: https://www.msif.org/about-us/who-we-are-and-what-we-do/advocacy/atlas/.
[6] Gaby A. Multiple sclerosis. Global Adv Health Med. 2013;2(1):50–6.
[7] Selmi C, Cincinelli G, Generali E, Dudam R, Ravindran V. Why women or why not men? Sex and autoimmune diseases. Ind J Rheumatol. 2018;13(1):44–50.
[8] Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016;16:626–38.
[9] Mahad D, Trapp B, Lassmann H. Pathological mechanisms in progressive multiple sclerosis. Lancet Neurol. 2015;14(2):183–93.
[10] Alkasir R, Li J, Li X, Jin M, Zhu B. Human gut microbiota: the links with dementia development. Protein Cell. 2016;8:90–102.
[11] Hu X, Wang T, Jin F. Alzheimer's disease and gut microbiota. Life Sci. 2016;59:1006–23.
[12] Saresella M, Mendozzi L, Rossi V, Mazzali F, Piancone F, La Rosa F, et al. Immunological and clinical effect of diet modulation of the gut microbiome in multiple sclerosis patients: a pilot study. Front Immunol. 2017;8:1391–402.
[13] La Rosa F, Clerici M, Ratto D, Occhinegro A, Licito A, Romeo M, et al. The gut-brain axis in Alzheimer's disease and omega-3. A critical overview of clinical trials. Nutrients. 2018;10:1267–84.
[14] Riccio P, Rossano R. Nutrition facts in multiple sclerosis. ASN Neuro. 2015;7(1):1–20.
[15] Bagur M, Murcia M, Jiménez-Monreal A, Tur J, Bibiloni M, Alonso G, et al. Influence of diet in multiple sclerosis: a systematic review. Adv Nutr. 2017;8(3):463–72.
[16] Katz Sand I. The role of diet in multiple sclerosis: mechanistic connections and current evidence. Curr Nutr Rep. 2018;7(3):150–60.
[17] Jahromi S, Toghae M, Jahromi M, Aloosh M. Dietary pattern and risk of multiple sclerosis. Iran J Neurol. 2012;11(2):47–53.
[18] Sedaghat F, Jessri M, Behrooz M, Mirghotbi M, Rashidkhani B. Mediterranean diet adherence and risk of multiple sclerosis: a case-control study. Asia Pac J Clin Nutr. 2016;25(2):377–84.
[19] Lucinda JB, Kimberley B, Anne-Louise P, Ingrid M, Robyn ML, Gavin P, et al. A higher mediterranean diet score, including unprocessed red meat, is associated with reduced risk of central nervous system demyelination in a case-control study of Australian adults. J Nutr. 2019: nxz089. doi:10.1093/jn/nxz089.
[20] Gan R, Young K, Zerbe G, Demoruelle M, Weisman M, Buckner J, et al. Lower omega-3 fatty acids are associated with the presence of anti-cyclic citrullinated peptide autoantibodies in a population at risk for future rheumatoid arthritis: a nested case-control study. Rheumatology. 2015;55(2):367–76.
[21] Calder P. Omega-3: the good oil. Nut Bulletin. 2017;42(2):132–40.
[22] Badsha H. Role of diet in influencing rheumatoid arthritis disease activity. Open Rheumatol J. 2018;12(1):19–28.
[23] Hidaka BH, Li S, Harve KE, Carlson SE, Sullivan DK, Kimler BF, et al. Omega-3 and omega-6 fatty acids in blood and breast tissue of high-risk women and association with atypical cytomorphology. Cancer Prev Res. 2015;8(5):359–64.
[24] Edwards I, O'Flaherty J. Omega-3 fatty acids and PPARγ in cancer. PPAR Res. 2008: 1–14.
[25] Jelinek G, Hadgkiss E, Weiland T, Pereira N, Marck C, van der Meer D. Association of fish consumption and omega-3 supplementation with quality of life, disability and disease activity in an international cohort of people with multiple sclerosis. Int J Neurosci. 2013;123(11):792–801.
[26] Ramirez-Ramirez V, Macias-Islas M, Ortiz G, Pacheco-Moises F, Torres-Sanchez E, Sorto-Gomez T, et al. Efficacy of fish oil on serum of TNFα, IL-1β, and IL-6 oxidative stress markers in multiple sclerosis treated with interferon beta-1b. Oxid Med Cell Longev. 2013: 1–8.
[27] Navarini L, Afeltra A, Gallo Afflitto G, Margiotta DPE. Polyunsaturated fatty acids: any role in rheumatoid arthritis? Lipids Health Dis. 2017;16(1):197.

[28] Sorto-Gomez ET, Ortiz GG, Fermín P, Pacheco-Moises F, Torres-Sánchez E, Ramirez-Ramirez V, et al. Effect of fish oil on glutathione redox system in multiple sclerosis. Am J Neurodegener Dis. 2016;5(2):145–51.
[29] Polman CH, Reingold CS, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69(2):292–302.
[30] McDonald WI, Compston DAS, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for MS: guidelines from the international panel on the diagnosis of MS. Ann Neurol. 2001;50(1):121–27.
[31] Polman CH, Reingold SC, Edan G. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald criteria". Ann Neurol. 2005;58(6):840–46.
[32] Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–73.
[33] Shamliyan T, Kane RL, Dickinson S. A systematic review of tools used to assess the quality of observational studies that examine incidence or prevalence and risk factors for diseases. J Clin Epidemiol. 2010;63:1061–70.
[34] Shamliyan T, Kane RL, Jansen S. Quality of systematic reviews of observational nontherapeutic studies. Prev Chronic Dis. 2010b;7:A133.
[35] Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. Br Med J. 2011;343:d5928.
[36] Woodward M. Sample size determination. In: Chapman & Hall, editor. Epidemiology: study design and data analysis. 2nd ed. London: CRC; 2005. p. 295–326.
[37] Whitley E, Ball J. Statistics review 4: sample size calculations. Crit Care. 2002;6:335–41.
[38] Williams JW, Plassman BL, Burke J, Benjamin S. Preventing Alzheimer's disease and cognitive decline. Evid Rep Technol Assess (Full Rep). 2010;193:1–72.
[39] Shinto L, Marracci G, Baldauf-Wagner S, Strehlow A, Yadav V, Stuber L, et al. Omega-3 fatty acid supplementation decreases matrix metalloproteinase-9 production in relapsing-remitting multiple sclerosis. Prostaglandins. Leukot Essent Fatty Acids. 2009;80(2–3):131–36.
[40] Pantzaris M, Loukaides G, Ntzani E, Patrikios I. A novel oral nutraceutical formula of omega-3 and omega-6 fatty acids with vitamins (PLP10) in relapsing remitting multiple sclerosis: a randomized, double-blind, placebo-controlled proof-of-concept clinical trial. BMJ Open. 2013;3(4):e002170.
[41] Bjørnevik K, Chitnis T, Ascherio A, Munger K. Polyunsaturated fatty acids and the risk of multiple sclerosis. Mult Scler. 2017;23(14):1830–38.
[42] Zandi-Esfahan S, Fazeli M, Shaygannejad V, Hasheminia J, Badihian S, Aghayerashti M, et al. Evaluating the effect of adding fish oil to Fingolimod on TNF-α, IL1β, IL6, and IFN-γ in patients with relapsing-remitting multiple sclerosis: A double-blind randomized placebo-controlled trial. Clin Neurol Neurosurg. 2017;163:173–78.
[43] Wergeland S, Torkildsen Ø, Bø L, Myhr KM. Polyunsaturated fatty acids in multiple sclerosis therapy. Acta Neurol Scand Suppl. 2012;195:70–5.
[44] Cunnane S, Ho S, Dore-Duffy P, Ells K, Horrobin D. Essential fatty acid and lipid profiles in plasma and erythrocytes in patients with multiple sclerosis. Am J Clin Nutr. 1989;50(4):801–6.