The Impact of Omega-3 Fatty Acids, Polyphenols and Vitamin D on Neurodegenerative Diseases: A Meta-Analysis*

Gözde YILDIZ**, Mehmet PALA***

Abstract

Aim: This study is aimed to to assess the impact of vitamin D, omega-3 fatty acids (ω-3), and polyphenols on cognitive functioning, clinical outcomes, and inflammatory biomarkers in patients diagnosed with Alzheimer's disease (AD), Parkinson's disease (PD), and Multiple Sclerosis (MS).

Method: A systematic search was conducted in the PubMed, Scopus, and Google Scholar databases. Only clinical trials and randomized controlled trials (RCTs) were included. A total of 689 studies published between 2000 and 2025 were reviewed, and 14 studies that met the inclusion criteria were analyzed. Effect sizes were calculated using Hedges' g value. Fixed and random effects models were used depending on heterogeneity. Funnel plots were used to assess publication bias. All statistical analyses were performed using the Comprehensive Meta-Analysis (CMA) program.

Results: Vitamin D supplementation significantly raised blood 25-hydroxyvitamin D [25(OH)D] levels (g = 1.589, p< .001). The Mini-Mental State Examination (MMSE) showed no significant cognitive effects of omega-3 polyunsaturated fatty acids and polyphenols (p> 0.05). One study indicated that ellagic acid reduced Expanded Disability Status Scale (EDSS) scores, while vitamin D and omega-3 supplementation did not. Some studies showed considerable reductions in IL-6 and TNF-α levels, but the meta-analysis found no statistical significance. A substantial decrease in TNF-α was seen in the fixed effects model (p= .0029), but not in the random effects model (p= .132)

Conclusion: Vitamin D supplementation markedly elevated serum 25(OH)D levels, indicating its potential as an effective intervention in neurodegenerative processes. The impact of omega-3 fatty acids and polyphenols on cognitive and clinical outcomes was observed to be inconsistent. Additional high-quality, long-term randomized controlled trials are necessary to more accurately assess the clinical efficacy of these compounds in neurodegenerative diseases.

Keywords: Vitamin D, omega-3 fatty acids, polyphenols, neurodegenerative diseases, meta-analysis.

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Omega-3 Yağ Asitleri, Polifenoller ve D Vitaminin Nörodejeneratif Hastalıklar Üzerindeki Etkisi: Bir Meta-Analiz

Öz

Amaç: Bu çalışmanın amacı, Alzheimer hastalığı, Parkinson hastalığı ve Multipl Skleroz tanısı almış bireylerde D vitamini, omega-3 yağ asitleri ve polifenollerin bilişsel fonksiyonlar, klinik sonuçlar ve inflamatuar biyobelirteçler üzerindeki etkilerini değerlendirmektir.

Yöntem: Scopus, PubMed ve Google Scholar veri tabanlarında sistematik bir arama yapıldı. Sadece klinik çalışmalar ve randomize kontrollü çalışmalar dahil edildi. 2000 ile 2025 yılları arasında yayınlanan toplam 689 çalışma incelendi ve dahil etme kriterlerini karşılayan 14 çalışma analiz edildi. Etki büyüklükleri Hedges'g değeri kullanılarak hesaplandı. Heterojenliğe bağlı olarak sabit ve rastgele etkiler modelleri kullanıldı. Yayın yanlılığını değerlendirmek için huni grafikleri kullanıldı. Tüm istatiksel analizler Comprehensive Meta-Analysis (CMA) programı kullanılarak yapılmıştır.

Bulgular: D vitamini takviyesi, kan 25-hidroksivitamin D [25(OH)D] seviyelerini önemli ölçüde yükseltti (g=1,589, p<,001). Mini-Mental Durum Testi, omega-3 çoklu doymamış yağ asitleri ve polifenollerin bilişsel açıdan önemli bir etkisini göstermedi (p>0,05). Bir çalışma, ellajik asidin Genişletilmiş Engellilik Durumu Ölçeği puanlarını düşürdüğünü, ancak D vitamini ve omega-3 takviyesinin düşürmediğini göstermiştir. Bazı çalışmalar IL-6 ve TNF-α seviyelerinde önemli düşüşler gösterdi, ancak meta-analiz istatiksel olarak anlamlı sonuç bulunamadı. Sabit etkiler modelinde TNF-α'da önemli bir azalma görülürken (p=,0029), rastgele etkiler modelinde görülmemiştir (p=,132).

Sonuç: D vitamini takviyesi serum 25(OH)D düzeylerini belirgin şekilde yükseltmiş, bu da nörodejeneratif süreçlerde etkili bir müdahale olarak potansiyelini göstermektedir. Omega-3 yağ asitlerinin ve polifenollerin bilişsel ve klinik sonuçlar üzerindeki etkisinin tutarsız olduğu gözlemlenmiştir. Bu bileşiklerin nörodejeneratif hastalıklardaki klinik etkinliğini daha doğru bir şekilde değerlendirmek için daha fazla, yüksek, kaliteli ve uzun vadeli randomize kontrollü çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: D vitamini, omega-3 yağ asitleri, polifenoller, nörodejeneratif hastalıklar, meta-analiz.

Introduction

Neurodegenerative diseases are illnesses characterized by structural and functional decline in different elements of the nervous system. The conditions impact both the central and peripheral nervous system. The conditions impact both the central and peripheral nervous systems, leading to substantial neurological impairments due to progressive neuronal loss[1]. According to the Global Burden of Disease (GBD) 2016 and 2021 reports, the global burden of neurological diseases, measured by the absolute number of disability-adjusted life years, continues to increase. The lack of modifiable risk factors in most neurological burdens indicates a need for new research to develop effective prevention and treatment strategies. 2016 GBD Alzheimer and other dementia diseases reports show that Türkiye its greatest age-standardized prevalence at 1192 cases per 100,000 population, followed by Brazil at 1038 (882-1220)[2,3]. It is estimated that there will be approximately 78 million individuals with dementia in 2030 and around 139 million in 2050[4]. The World Federation of Neurology (WFN) emphasizes the importance of risk assessment, proactive prevention, and early diagnosis in the management of neurological disorders. However, neurological conditions caused by environmental and genetic factors can be prevented by identifying and eliminating these

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risks[5]. Modifiable risk factors such as malnutrition, obesity, alcohol consumption, smoking, vitamin D deficiency, social isolation, physical inactivity are associated with the onset and progression of major and mild neurocognitive disorders[6,7]. Research shows that nutrition and lifestyle factors have a significant impact on neurological health, cognitive decline, and slowing the progression of neurological diseases[8]. These findings suggest that nutrients such as vitamin D[9], B vitamins[10], omega-3 fatty acids[11], polyphenols[12,13], folic acid and antioxidants may protect cognitive function[14].

This study examines three main neurodegenerative diseases: Alzheimer's disease (AD), Parkinson's disease (PD) and Multiple Sclerosis (MS). These findings may guide dietary therapies and healthy aging support. Clinicians and nutritionists may use this information to build effective dietary therapies to improve cognition and postpone neurodegeneration. The data may also help establish evidence-based methods to promote healthy aging and reduce AD, PD, and MS in aging populations.

Material and Methods

Study Design

This study aims to systematically evaluate the relationship between nutrition and cognitive function in patients with AD, MS and PD diagnoses through meta-analysis. The study followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)[15] guidelines and was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO)[16] database (Registration ID: CRD420251036619).

Literature Strategy

The main databases searched were PubMed, Scopus and Google Scholar. Original and methodological search strategies were used for each database to fit the investigation. All studies found during the literature search were tagged with a number and their basic information was included into a structured Excel spreadsheet for this systematic review. Each study was re-evaluated after data coding and eliminated if it did not fit the inclusion and exclusion criteria. Through database research, total 689 studies were examined and 14 study included meta-analysis. A PRISMA flow diagram shows the full selection process (Figure 1).

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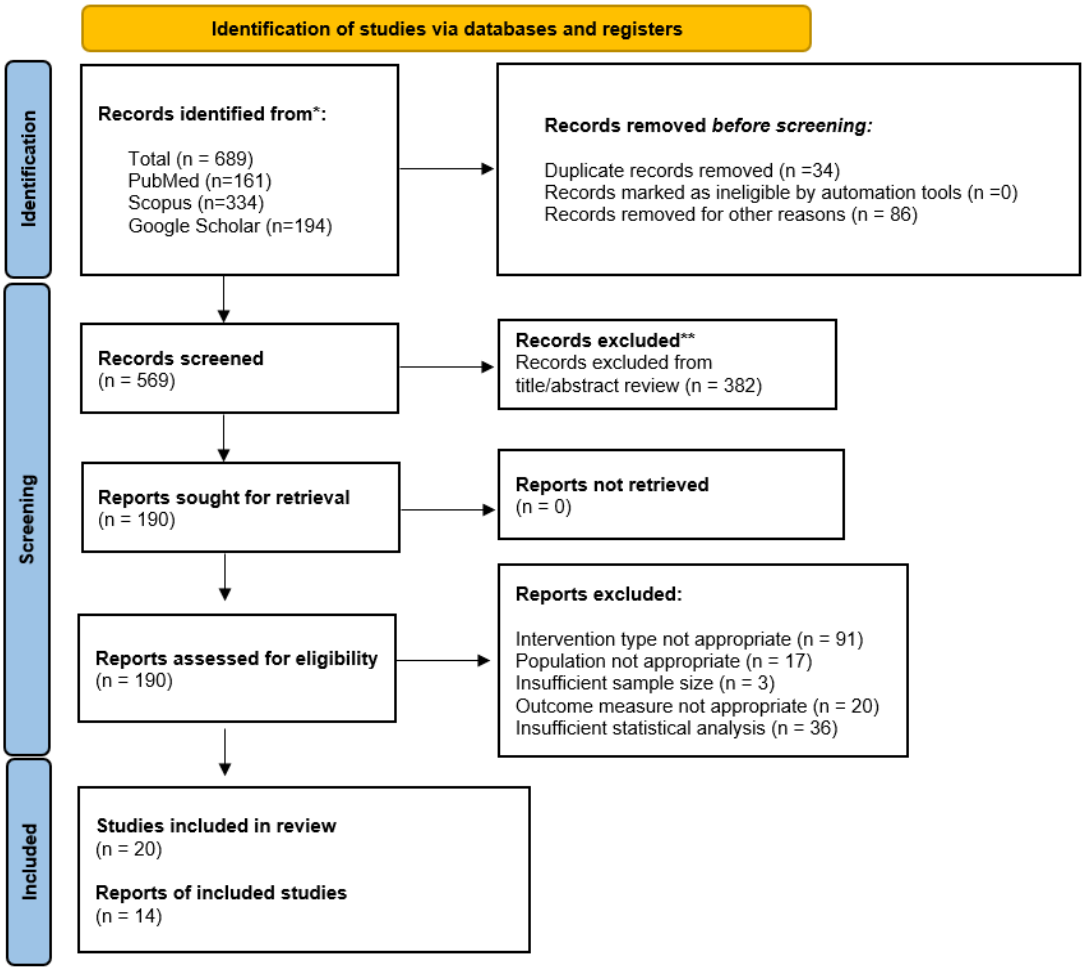
Figure 1. PRISMA 2020 flow diagram depicting the research selection procedure.



Inclusion and Exclusion Criteria

This study included RCT, and clinical studies conducted on human participants diagnosed with AD, PD, and MS. Only studies that investigated a single nutritional intervention-vitamin D, omega-3 fatty acids, or polyphenols- and reported clinical, cognitive, or biomarker outcomes in a format suitable for meta-analysis (mean ± SD) were included.

Studies were excluded if they:

- Involved animal models or cell lines,
- Targeted healthy individuals without neurodegenerative conditions
- Included pharmacological or combined interventions unrelated to diet,
- Reported irrelevant outcomes (e.g. weight loss)
- Lacked proper statistical data or methodological clarity,

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- Had small sample sizes (n<10)
- Were not clinical trials
- Were published in languages other than English or Turkish

Outcome Measures

The outcome measures evaluated in the studies included the Expanded Disability Status Scale (EDSS), Mini Mental State Examination (MMSE) neuropsychological assessments, and biochemical markers such as 25(OH)D, Interleukin-6 (IL-6), and Tumor Necrosis Factor-Alpha (TNF-α).

Statistical Analysis

Hedges' g effect sizes were calculated for each study by taking the sample size, mean, and standard deviation values for the experimental and control groups. Hedges' g was preferred because it contains less bias in effect size estimates, especially in studies with small sample sizes. Prior to the meta-analysis, Cochran's Q test, I^2 statistic, and τ^2 variance were calculated to identify methodological differences among the studies. In variables with high I2 value analyses were conducted using a random effects model, taking into account statistical heterogeneity. Funnel plots were created for each variable to assess the likelihood of publication bias. The meta-analysis results were evaluated on a variable basis, and the obtained effect sizes, confidence intervals, and significance levels were interpreted both statistically and in a clinical context. Comprehensive Meta-Analysis (CMA) was used to analyze the data during the research process[17,18].

Results

Of the 689 articles examined, 14 fulfilled the inclusion criteria and were incorporated into the meta-analysis. Every research included provided comprehensive quantitative data, encompassing sample size (N), mean values (μ), and standard deviations (σ) for both intervention and control groups. These quantitative data were analyzed within the scope of the meta-analysis to assess and compare the effects of each type of nutritional supplement on the specified neurodegenerative diseases. The analysis of studies assessing the influence of vitamin D, omega-3 fatty acids, and ellagic acid on EDSS scores in MS patients produced a non-significant effect size (g= -0.495, SE= 0.372, 95% CI: [1.225, 0.234], z= -1.33, p= .183). The examination of MMSE scores in AD and Mild Cognitive Impairment (MCI) population revealed a minor yet statistically insignificant effect, indicating the limited efficacy of omega-3 and polyphenol supplementation on cognitive performance (g= 0.150, SE= 0.124, CI: [0.092, 0.392], z= -1.215, p= .224). Vitamin D supplementation markedly elevated blood 25(OH)D levels with effect size and little between-study variation (τ^2= 0.058), signifying consistency in the results (g= 1.589, SE= 0.241, 95% CI: [1.117, 2.061], z= 6.598, p= .001). The influence of omega-3 fatty acids and polyphenol supplementation on IL-6 levels was not statistically significant (g= -1.241, SE= 0.939, 95% CI: [-3.082, 0.600], z= -1.321, p= 0.187). Likewise, the effect of

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omega-3 and vitamin D supplementation on TNF-α levels did not achieve significance (g= -1.959, SE= 1.301, 95% CI: [-4.509, 0.591], z= -1.506, p= 0.132). The basis attributes of the studies considered are encapsulated in Table 1.

Table 1. Characteristics of studies included in the meta-analysis.

				Intervention Group			**Control Group**		
Outcome Measure	**Research**	**Intervention Type**	**Disease**	**N**	**μ**	**σ**	**N**	**μ**	**σ**
EDSS	Jafari Karegar et al., 2023	Ellagic Acid	MS	25	1.54	.32	25	2.62	.29
	Camu et al., 2019	Cholecalciferol	MS	45	1.60	1.63	45	1.54	1.45
	Mosayebi et al., 2011	Vitamin D	MS	26	2.31	1.30	33	2.67	1.25
	Torkildsen et al., 2012	Omega-3	MS	46	2.22	1.32	45	2.19	1.34
	Ramirez-Ramirez et al., 2013.	Vitamin D	MS	20	2.20	1.00	19	2.20	.80
	Kampman et al., 2012		MS	35	2.77	1.18	33	2.42	1.19
MMSE	Chiu et al., 2008	Omega-3	Alzheimer and MCI	17	25.47	3.81	12	25.09	3.67
	Loukou et al., 2024	Polyphenol	Alzheimer	13	2.40	3.70	10	18.80	4.50
	Freund-Levi et al., 2006	Omega-3	Alzheimer	89	22.10	4.81	85	21.90	4.93
	Tofiq et al., 2021	Omega-3	Alzheimer	18	24.20	4.11	15	21.60	4.14
25(OH)D	Bytowska et al., 2023	Vitamin D	Parkinson	15	34.12	1.75	21	18.38	11.98
	Jia J, et al., 2019	Vitamin D	Alzheimer	105	22.77	3.41	105	19.08	2.84
	Røsjø et al., 2015	Vitamin D	MS	36	49.36	13.7	32	25.28	9.78
	Kampman MT et al. 2012	Vitamin D	MS	35	49.35	12.32	33	24.76	12.32

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IL-6	Ramirez-Ramirez, et al. 2013. Bytowska et al., 2023 Tofiq et al., 2021 Freund-Levi et al., 2009	Omega-3 Vitamin D Omega-3 Omega-3	MS Parkinson Alzheimer Alzheimer	20 15 17 18	356.7 1.98 3.12 3.30	31.7 .87 1.19 1.41	19 21 15 17	644.6 2.35 2.71 2.70	57.3 1.45 .90 .84
TNF- α	Ramirez-Ramirez et al., 2013. Bytowska et al., 2023 Freund-Levi et al., 2009	Omega-3 Vitamin D Omega-3	MS Parkinson Alzheimer	20 15 18	22.70 5.98 .25	2.40 2.09 .330	19 21 17	39.10 7.23 .18	3.10 1.94 .210

Table 2 represents the outcomes of homogeneity assessments performed before the meta-analysis. The tests were conducted to ascertain the presence of statistically significant heterogeneity among the included studies. The I^2 values indicate the percentage of variance attributed to actual differences among studies, while the Q and p-values reflect the significance of heterogeneity[17]. According to the results, high heterogeneity (I^2>85%) was observed in EDSS, IL-6, TNF-α, IFN-γ, and TGF-β outcomes, which was statistically significant (p<.05). The 25 (OH)D outcome showed moderate heterogeneity (I^2 = %70.722; p =.017). In contrast, MMSE and ADAS-Cog outcomes showed no significant heterogeneity among studies (I^2=.000; p>.05).

Table 2. Homogeneity test results prior to meta-analysis

		Tau²	**Q**	**SD**	**I²**	**p**
Effects of Vitamin D, Omega-3, and Polyphenol Supplements on Cognitive Function or Biomarkers in Patients who Alzheimer's, Parkinson's, or Multiple Sclerosis	EDSS	.750	61.167	5	91.826	.000*
	MMSE	.000	2.663	3	.000	.447
	25(OH)D	.167	10.247	3	70.722	.017*
	IL-6	3.467	67.773	3	95.573	.000*
	TNF- α	5.050	57.338	2	96.512	.000*

Meta-analysis results by outcome categories are shown in Table 3. Analysis using a random effects model was utilized to address inter-study variability.

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Table 3. Results of meta-analysis.

							%95 Confidence Interval (CI)			
	Study	**Intervention Type**	**Disease**	**Hedges's g**	**Standard Error**	**Variance**	**Lower Limit**	**Upper Limit**	**z**	**p**
EDSS	Jafari Karegar et al., 2023	Ellagic Acids	MS	-3.481	.446	.199	-4.355	-2.608	-7.81	**.000**
	Camu et al., 2019	Vitamin D	MS	.039	.209	.044	-.371	.448	.184	.854
	Mosayebi et al., 2011	Vitamin D	MS	-.279	.260	.068	-.789	.230	-1.074	.283
	Torkildsen et al., 2012	Omega-3	MS	.022	.208	.043	-.385	.430	.108	.914
	Ramirez-Ramirez et al., 2013.	Omega-3	MS	.000	.314	.098	-.615	.615	.000	1.00
	Kampman et al., 2012	Vitamin D	MS	.292	.241	.058	-.181	.765	1.211	.226
		Fixed Effects		-.163	.104	.011	-.366	.040	-1.578	.115
		Random Effects		-.495	.372	.139	-1.225	.234	-1.33	.183
MMSE	Chiu et al., 2008	Omega-3	Alzheimer and MCI	.098	.367	.134	-.62	.817	.268	.788
	Loukou et al., 2024	Polyphenol	Alzheimer	.380	.409	.167	-.423	1,182	.928	.354
	Freund-Levi et al., 2006	Omega-3	Alzheimer	.041	.151	.023	-.255	.337	.271	.787
	Tofiq et al., 2021	Omega-3	Alzheimer	.615	.349	.122	-.070	1.300	1.761	.078
		Fixed Effects		.150	.124	.015	-.092	.392	1.215	.224
		Random Effects		.150	.124	.015	-.092	.392	1.215	.224
25(OH)D	Bytowska et al., 2023	Vitamin D	Parkinson	1.340	.366	.134	.622	2.057	3.657	**.000**
	Jia J, et al., 2019	Vitamin D	Alzheimer	1.172	.149	.022	.880	1.464	7.867	**.000**
	Røsjø et al., 2015	Vitamin D	MS	1.981	.294	.087	1.404	2.557	6.733	**.000**
	Kampman et al. 2012	Vitamin D	MS	1.973	.294	.086	1.398	2.549	6.722	**.000**
		Fixed Effects		1.435	.115	.013	1.209	1.66	12.482	**.000**
		Random Effects		1.589	.241	.058	1.117	2.061	6.598	**.000**
IL-6	Ramirez-Ramirez et al. 2013	Omega-3	MS	-6.135	.762	.581	-7.629	-4.641	-8.049	**.000**
	Bytowska et al., 2023	Vitamin D	Parkinson	-.291	.332	.11	-.942	.361	-.875	.382
	Tofiq et al., 2021	Omega-3	Alzheimer	.375	.348	.121	-.308	1.058	1.077	.281
	Freund-Levi et al., 2009	Omega-3	Alzheimer	.502	.336	.113	-.157	1.16	1.493	.135
		Fixed Effects		-.203	.189	.036	-.574	.168	-1.071	.284
		Random Effects		-1.241	.939	.883	-3.082	.6	-1.321	.187
TNF-α	Ramirez-Ramirez et al., 2013.	Omega-3	MS	-5.815	.729	.532	-7.244	-4.385	-7.972	**.000**
	Bytowska et al., 2023	Vitamin D	Parkinson	-.61	.338	.114	-1.273	.053	-1.804	.071
	Freund-Levi et al., 2009	Omega-3	Alzheimer	.246	.332	.11	-.405	.896	.741	.459
		Fixed Effects		-.712	.225	.051	-1.154	-.27	-3.161	.002
		Random Effects		-1.959	1.301	1.692	-4.509	.591	-1.506	.132

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Discussion

The meta-analysis results indicate that dietary treatments, vitamin D, omega-3 fatty acids, and polyphenols, have a minor and statistically insignificant overall effect on EDSS scores in patients with MS. A significant degree of variability was noted among the trials, likely arising from variations in intervention kinds, doses, durations, and patient demographics. As the confidence interval encompasses zero, no conclusive determination can be made about the effect's direction. The funnel plot indicated that the data distribution was predominantly symmetric, while a few small-sample studies were located outside the funnel limits. This indicates a little risk of publishing bias; nonetheless, most data points fell within the anticipated range, suggesting no significant systematic bias. The forest plot demonstrated that the effect sizes were broadly heterogeneous and failed to reach statistical significance. These general findings were also supported by individual study results. For instance, the triple-blind RCT by Jafari Karegar et al. (2023) reported a significant reduction in EDSS scores with ellagic acid supplementation, whereas Mosayebi et al. (2011) found no meaningful change with high-dose vitamin D. Similarly, Torkildsen (2012) and Ramirez-Ramirez (2013) found no substantial impact of omega-3 fatty acid supplementation. The investigations conducted by Kampman et al. (2012) and Camu et al. (2019) revealed that the benefits of vitamin D were minimal, with clinical results predominantly linked to enhancements in immunological markers. Collectively, these findings suggest that dietary supplementation does not yield a definitive clinical advantage on EDSS scores in the short or medium term. Nonetheless, methodological constraints in the existing literature – such as small sample numbers, brief follow-up durations, and inadequate sensitivity of outcome measures – underscore the necessity for future randomized controlled trials with bigger cohorts and more stringent designs[19–24].

The MMSE was employed to assess the effects of therapies on cognitive performance in patients diagnosed with Alzheimer's disease and MCI. Along with this, the meta-analysis indicated a minor and statistically insignificant overall effect size. The homogeneity test revealed no significant heterogeneity, and the funnel plot demonstrated no evidence of publication bias, so affirming the dependability of the data. Although the interventions showed a trend toward positive effects on cognitive maintenance, these were not statistically significant. Moreover, it is possible that general cognitive tools like MMSE may have limited sensitivity in detecting short-term changes following nutritional interventions. At the individual study level, Loukou et al. (2024) reported a significant improvement in cognitive preservation using olive leaf extract in the GOLDEN trial. Tofiq et al. (2021) observed a protective effect of omega-3 supplementation on MMSE scores. In contrast, Chiu and Freund-Levi et al. (2006) did not find significant effects in general AD populations, although early-stage patients showed a trend toward cognitive benefit. These findings suggest that nutritional supplementation may provide cognitive support particularly in early-stage AD or with certain bioactive compounds, though larger and longer-term RCTs are required to confirm these effects[25–28].

The meta-analysis showed that vitamin D supplementation significantly and consistently increased serum 25(OH)D levels in individuals with Parkinson's, Alzheimer's, and MS.

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The large overall effect size and confidence intervals above zero suggest both statistical and clinical significance. While study heterogeneity was moderate, asymmetry in the funnel plot and missing data on the left side raise concerns about potential publication bias, warranting cautious interpretation. Several studies have associated low 25(OH)D levels with dementia, motor dysfunction, and cognitive decline. Vitamin D is believed to exert neuroprotective effects through its neurosteroid properties, immune modulation, and antioxidant capacity. Study-level data also support this: Bytowska et al. (2023) reported a notable rise in 25(OH)D levels and a concurrent decline in 3-hydroxykynurenine among Parkinson's patients. Røsjø (2015) and Kampman (2012) similarly demonstrated significant rises in serum 25(OH)D, although without substantial changes in inflammatory biomarkers or clinical MS outcomes[23,29–31].

In terms of inflammatory biomarkers, the meta-analysis did not show substantial effects of the interventions on IL-6 or TNF-α levels. Although some individual studies, such as Ramirez-Ramirez et al., (2013) observed reductions in these markers following omega-3 or vitamin D supplementation, the overall pooled effects were statistically non-significant and marked by high heterogeneity. Funnel plot asymmetry further raised concerns about potential publication bias. These findings may reflect the complexity of neuroinflammatory pathways and the limited responsiveness of these cytokines to short-term nutritional interventions[21,28,29,32].

These findings confirm that Vitamin D intake effectively raises serum 25(OH)D, yet this biochemical improvement does not always translate into clear clinical or immunological outcomes. Future RCTs with established methods and extended follow-up durations are needed to explore these relationships further.

Strengths and Limitations

Our study employed a meticulous systematic process; however, the main limitation arising from this was that only 14 studies out of the 689 articles initially screened could be included in the meta-analysis. The main reason for the high exclusion rate is the extremely strict criteria we applied to maximize the scientific validity of the study. The vast majority of excluded studies were excluded because they were not RCTs, were animal studies, or were review articles. Following this, the next most common reasons for exclusion were inappropriate intervention type and lack of data necessary for statistical analysis. Although this limits the generalizability of our results and indicates that the evidence base in the field under review is still insufficient to meet strict methodological requirements, this rigorous selection process has ensured that the 14 included studies are of the highest methodological quality. Consequently, this has significantly increased the internal validity and reliability of the combined effect size we obtained, forming the strength of our study. Our findings, therefore, strongly reiterate the ongoing need for well-designed, large-scale RCTs in the field to provide conclusive and generalizable evidence.

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Conclusion

This meta-analysis assessed the impact of vitamin D, polyphenols and omega-3 fatty acids on individuals who have Alzheimer's, Parkinson's, and Multiple Sclerosis, focusing on clinical and cognitive outcomes measured by EDSS and MMSE, as well as biomarkers of inflammation including IL-6, TNF-α, and 25(OH)D. The findings indicated that these dietary components generally had limited and often statistically non-significant effects on clinical and cognitive outcomes. However, studies involving vitamin D intake demonstrated significant increases in serum 25(OH)D levels, and some interventions with omega-3 fatty acids and polyphenols were associated with beneficial changes in IL-6 and TNF-α levels. Since the meta-analyses for ADAS-Cog, IFN-γ, and TGF-β included only two studies each, these specific results should be interpreted with caution. Based on these findings, future research should involve larger sample sizes, standardization of parameters such as intervention duration and dosage, and clear reporting to enhance the power of meta-analysis. Expanding biomarker-based studies, integrating clinical symptoms with cognitive and neurobiological outcomes, and considering nutritional interventions as complementary to pharmacological treatments may contribute to a more comprehensive understanding. In addition, future systematic reviews should consider subgroup analyses based on disease stages, age groups, and disease subtypes to provide more nuanced insights.

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