Role of omega-3 fatty acids in reducing proteinuria: A systematic review and meta-analysis

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Running title: Role of omega-3 in reducing proteinuria

Liangyu Fei[1†], Rizhen Huang[2†], Zhong Li[3]

[1]The Affiliated Nanhua Hospital, Department of Nephrology, Hengyang Medical School, University of South, Hunan, China.
[2]Department of Nephropathy Rheumatism, Hainan Traditional Chinese Medicine Hospital, Hainan, China.
[3]Department of Nephrology, West China Fourth Hospital, Sichuan University, Si Chuan, China.
[†]Both authors contributed equally to this manuscript

Authors' email addresses and contributions:
LF: feiliangyu123456@sina.com
Contribution: undertook data collection and data analysis, and contributed to data interpretation, and writing the manuscript.

RH: huangrizhen1234@sina.com
Contribution: undertook data collection and data analysis, and contributed to data interpretation, and writing the manuscript.

ZL: lizhong2022@sina.com
Contribution: conceived the study question, and contributed to the study design, supervision of data collection, data analysis and interpretation, and writing the manuscript.

Corresponding Author: Dr Zhong Li, Department of Nephrology, West China Fourth Hospital, Sichuan University, Chengdu, Si Chuan, 610041, China. Tel: . Email: lizhong2022@sina.com

ABSTRACT

Background and Objectives: Proteinuria, a hallmark of renal and systemic disorders, is associated with adverse outcomes, especially in chronic kidney disease and cardiovascular disease. Omega-3 fatty acids have garnered attention for their cardiovascular benefits and potential therapeutic effects on proteinuria. This systematic review and meta-analysis aimed to evaluate the impact of omega-3 fatty acid supplementation on proteinuria levels across various kidney-related conditions. **Methods and Study Design:** Studies published from 1989 to 2023 were systematically identified, including randomized controlled trials, cohort, case-control, and cross-sectional studies. Nine studies involving a total of 347 participants were included in the analysis. **Results:** The meta-analysis revealed a neutral overall effect size of omega-3 fatty acid supplementation on proteinuria levels, assessed under both common and random effect models. Despite the lack of statistically significant evidence supporting the efficacy of omega-3 fatty acids in reducing proteinuria, the variability in interventions and patient populations suggests potential individual responses. **Conclusions:** The findings highlight the heterogeneity in responses to omega-3 fatty acid supplementation and emphasize the need for cautious interpretation. While no definitive conclusion can be drawn, the results underscore the importance of targeted research focusing on specific subgroups or conditions that may benefit from omega-3 supplementation. These findings contribute to the evolving understanding of personalized kidney health strategies and pave the way for further exploration and optimization of omega-3 fatty acids' therapeutic applications.

Key Words: Omega-3 fatty acids, proteinuria, chronic kidney disease, randomized controlled trials, meta-analysis

INTRODUCTION

Proteinuria, characterized by the presence of excessive protein in urine, stands as a hallmark of numerous renal and systemic disorders.[1] Beyond its diagnostic value, proteinuria serves as a potent predictor of adverse clinical outcomes, particularly in the context of chronic kidney disease (CKD) and cardiovascular disease (CVD).[2] Elevated urinary protein levels not only signify underlying renal injury but also herald increased risks of kidney function decline, end-stage renal disease (ESRD), and cardiovascular events.[3,4] The importance of identifying effective strategies to mitigate proteinuria and its associated risks cannot be overstated.

In the quest for therapeutic interventions to ameliorate proteinuria, Omega-3 fatty acids have garnered substantial attention.[5] Omega-3 fatty acids, predominantly found in fish oils

and certain plant sources, have long been recognized for their cardiovascular benefits, primarily attributed to their anti-inflammatory and anti-atherogenic properties.[6,7] Beyond their established role in cardiovascular health, emerging evidence suggests that Omega-3 fatty acids may exert a favorable impact on renal function, particularly in the context of proteinuria.[8,9]

The potential therapeutic utility of omega-3 fatty acids in reducing proteinuria stems from their multifaceted mechanisms of action.[10] These bioactive lipids are known to modulate inflammatory responses, oxidative stress, and the renin-angiotensin-aldosterone system, all of which are intricately involved in renal pathology.[11] Additionally, omega-3 fatty acids may influence glomerular and tubular function, ultimately affecting protein filtration and reabsorption processes.[12]

While individual studies and clinical trials have investigated the effects of omega-3 fatty acids on proteinuria, the collective body of evidence has yet to be systematically synthesized and rigorously evaluated. A comprehensive review and meta-analysis of available studies are warranted to elucidate the potential role of omega-3 fatty acids in reducing proteinuria and its associated clinical implications.

This systematic review and meta-analysis aim to fill this crucial knowledge gap by synthesizing existing evidence. Through an exhaustive examination of relevant literature, encompassing clinical trials and observational studies, we seek to assess the impact of omega-3 fatty acid supplementation on proteinuria levels. Furthermore, we aim to explore potential mechanisms underlying any observed effects and offer insights into the clinical relevance of omega-3 fatty acids in the management of proteinuria.

MATERIALS AND METHODS

Search strategy and data sources

To conduct a comprehensive systematic review, we systematically searched electronic databases, including PubMed, Embase, Scopus, and the Cochrane Library. The search encompassed studies published up to September 2023, and no lower date limit was applied. Our search strategy employed a combination of keywords and medical subject headings (MeSH) related to omega-3 fatty acids, proteinuria, and relevant synonyms. The search strategy was developed with the assistance of a skilled medical librarian to ensure inclusivity and comprehensiveness. We also reviewed the reference lists of included articles and relevant systematic reviews for any additional eligible studies.

Inclusion criteria

Study Design: Randomized controlled trials (RCTs), cohort studies, case-control studies, and cross-sectional studies were considered for inclusion. Studies that assessed the administration of omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), either as supplements or dietary sources, were eligible.

The primary outcome of interest was the change in proteinuria levels as measured by 24-hour urinary protein excretion.

Exclusion criteria

Studies not reporting relevant outcomes or not involving Omega-3 fatty acid interventions.

Animal studies, reviews, editorials, and conference abstracts, studies with insufficient data for quantitative analysis, duplicate publications or secondary analyses of the same study population.

Study selection and data extraction

Two independent reviewers (insert names or initials) conducted the initial screening of titles and abstracts to identify potentially eligible studies. Subsequently, full-text articles of selected studies were reviewed for final inclusion. Discrepancies in study selection were resolved through discussion or consultation with a third reviewer (insert name or initials) when necessary.

Assessment of methodological quality and risk of bias

For RCTs, the Cochrane Risk of Bias Tool was used to assess the methodological quality of included studies. Cohort and case-control studies were evaluated using the Newcastle-Ottawa Scale.[13] Cross-sectional studies were assessed using relevant criteria adapted from established tools. Risk of bias assessment was conducted independently by two reviewers, and any discrepancies were resolved through discussion.

Data synthesis and statistical analysis

Meta-analysis was conducted using appropriate statistical software (STATA version 12) following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] For continuous outcomes, standardized mean differences (SMD) with 95% confidence intervals (CI) were calculated to account for variations in measurement scales among studies. Heterogeneity between studies was assessed using the I^2 statistic, with

I2 > 50% indicating substantial heterogeneity. A random-effects model was used when significant heterogeneity was present; otherwise, a fixed-effects model was applied. Sensitivity analyses and subgroup analyses were planned to explore potential sources of heterogeneity. Publication bias was assessed using funnel plots, Egger's test, and the fail-safe N method.

RESULTS

Through our exploration of the database, a total of 562 records were identified. Following the removal of 241 duplicate entries, we proceeded to evaluate the titles and abstracts of the remaining 321 records. Subsequently, 152 papers were excluded based on predetermined criteria, leaving us with 71 studies for comprehensive full-text assessment. During this phase, two records were excluded in accordance with our eligibility criteria. Ultimately, our meta-analysis incorporated a total of nine studies, as illustrated in Figure 1.

Study characteristics

Table 1 summarizes the key characteristics of the included studies. A total of ten studies were identified for inclusion in this systematic review and meta-analysis. These studies were published between 1989 and 2015, reflecting research conducted in various countries, including Greece, Italy, Japan, the USA, Sweden, and Australia. The sample sizes across these studies ranged from 19 to 54 participants, with a total of 347 participants included in the analysis. The primary focus of these studies was on the impact of omega-3 fatty acids in the context of kidney diseases, particularly IgA nephropathy, ADPKD (autosomal dominant polycystic kidney disease), chronic kidney disease (CKD) and diabetic nephropathy. The duration of intervention varied among studies, ranging from 2 months to 4 years.

Intervention and control groups

The interventions utilized in the included studies were diverse. Some studies employed eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA) as the primary omega-3 fatty acids, with doses ranging from 1.8 g/day to 12 g/day. Additionally, some studies combined omega-3 supplementation with renin-angiotensin system blockers (RASB), angiotensin-converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB) as part of the intervention. Control groups, on the other hand, received placebo treatments, olive oil, supportive care, or no treatment, depending on the study design. The choice of control intervention was tailored to the specific research objectives of each study.

Disease status and JADAD scores

The studies primarily focused on kidney-related conditions, with a particular emphasis on IgA nephropathy. The included studies evaluated participants with IgA nephropathy, ADPKD, or CKD. The JADAD scores, a measure of study quality, ranged from 2 to 4, indicating a moderate to high level of methodological quality across the studies.[15] These scores reflect the rigor of randomized controlled trial (RCT) designs, which are robust for assessing the efficacy of interventions.

Duration of interventions

The duration of omega-3 fatty acid interventions varied across studies. Some investigations spanned over a course of 2 months, while others extended up to 4 years. These variations in intervention duration provide insights into the potential short-term and long-term effects of omega-3 fatty acid supplementation in the context of kidney diseases.

Effect Size Estimation

The meta-analysis was conducted using both fixed and random effect models. The standardized mean difference (SMD) values along with their corresponding 95% confidence intervals (CI) were calculated for each study. The results are summarized in Figure 2.

Overall effect size

Under the common effect model, the overall effect size (SMD) was estimated to be 0.0599 (95% CI [-0.2054; 0.3252]), indicating a non-significant effect (z = 0.44, p = 0.6582). Similarly, under the random effects model, the overall effect size was -0.1600 (95% CI [-1.5526; 1.2326]), also indicating a non-significant effect (z = -0.27, p = 0.7937).

Heterogeneity

Substantial heterogeneity was observed among the included studies. The estimated between-study variance (tau^2) was 2.4473 (95% CI [0.9532; 11.7919]), corresponding to a tau value of 1.5644 (95% CI [0.9763; 3.4339]). The I^2 statistic, representing the percentage of variation attributed to heterogeneity, was 91.1% (95% CI [84.9%; 94.8%]), and the H statistic was 3.35 (95% CI [2.57; 4.37]), both indicating substantial heterogeneity.

A test of heterogeneity (Q) resulted in a significant p-value of < 0.0001 (Q = 78.74, degrees of freedom = 7), further confirming the presence of significant heterogeneity.

Publication Bias

Publication bias was assessed using the Egger's Regression Test, and the results suggested that there might be publication bias. However, the number of studies included in the analysis was less than the recommended threshold of nine for a more valid assessment of publication bias.

Funnel Plot (Trim and Fill)

The funnel plot analysis did not reveal any potential publication bias. The results of the linear regression test of funnel plot asymmetry showed a *p*-value of 0.4012.(Figure 3).

DISCUSSION

Our systematic review and meta-analysis involved a comprehensive exploration of the role of omega-3 fatty acids in reducing proteinuria by analyzing data from a diverse set of studies. This approach allowed us to gain insights from research conducted across different countries and settings. The diversity in study populations and settings contributes to the robustness of our analysis, offering a broad perspective on the potential benefits of omega-3 fatty acid supplementation in proteinuria management.

One of the striking aspects of our analysis was the variability in the intervention approaches adopted across the included studies. Omega-3 fatty acids encompass various forms, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The doses administered ranged from 1.8 g/day to 12 g/day, reflecting a spectrum of treatment regimens. Furthermore, several studies combined omega-3 supplementation with renin-angiotensin system blockers (RASB), angiotensin-converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB) as part of the intervention strategy. In contrast, control groups received diverse control interventions, such as placebo treatments, olive oil, supportive care, or no treatment. The versatility of intervention approaches underscores the multifaceted nature of omega-3 fatty acid supplementation and its potential for customization based on the specific objectives of each study.

The primary medical conditions under scrutiny in the included studies were kidney-related diseases, with an emphasis on IgA nephropathy. This focus reflects the growing interest in exploring the therapeutic effects of omega-3 fatty acids in managing proteinuria in the context of nephropathies. Additionally, studies assessed participants with ADPKD and CKD, and diabetic nephropathy broadening the scope of conditions examined.

The assessment of study quality using JADAD scores revealed that the included studies demonstrated a moderate to high level of methodological quality. These scores reflect the rigorous nature of randomized controlled trial (RCT) designs, widely recognized for their robustness in assessing the efficacy of interventions.

The duration of omega-3 fatty acid interventions varied significantly among the studies. Some investigations focused on short-term interventions lasting only 2 months, while others extended over a span of 4 years. This diversity in intervention durations provides valuable insights into the potential short-term and long-term effects of omega-3 fatty acid supplementation in the context of proteinuria management. It is essential to consider the implications of these varying durations when interpreting the findings, as they may inform clinical recommendations regarding the optimal duration of omega-3 fatty acid supplementation.

Our meta-analysis, employing both fixed-effect and random-effects models, provided estimates of the overall effect size of omega-3 fatty acids on proteinuria reduction. However, it's noteworthy that under both models, the overall effect sizes were not statistically significant, indicating a neutral effect. These findings suggest that, as a whole, the studies included in our analysis did not demonstrate a substantial impact of omega-3 fatty acid supplementation on proteinuria reduction.

Nonetheless, the clinical significance of these results should not be dismissed outright. It is important to recognize that individual responses to omega-3 fatty acids may vary, and factors such as dosage, duration, and patient characteristics may influence outcomes. Additionally, while our meta-analysis may not have shown a significant overall effect, it is possible that specific subgroups of patients or particular conditions may benefit from omega-3 fatty acid supplementation. Therefore, the neutral overall effect size should not discourage further exploration and research into the potential use of omega-3 fatty acids as part of comprehensive proteinuria management strategies.

A significant challenge in our analysis was the substantial heterogeneity observed among the included studies, as indicated by high I^2 and H statistics. This heterogeneity may stem from differences in patient populations, variations in intervention protocols, and diverse control interventions employed across the studies. It underscores the need for cautious interpretation of the overall effect size and emphasizes the importance of investigating potential sources of heterogeneity in future research.

Our assessment of publication bias yielded mixed results. While Egger's Regression Test suggested the possibility of publication bias, the funnel plot analysis did not reveal obvious

signs of such bias. It is essential to acknowledge that the number of studies included in our analysis fell short of the recommended threshold for a robust assessment of publication bias. Therefore, the implications of potential publication bias should be interpreted with caution.

Future research should prioritize investigating specific patient profiles that may derive the most substantial benefit from omega-3 fatty acid supplementation. Additionally, the optimization of dosage, duration, and timing of omega-3 fatty acid interventions should be explored within comprehensive proteinuria management strategies. As our understanding of the intricate relationship between omega-3 fatty acids and proteinuria continues to evolve, it opens doors to personalized therapeutic approaches that may contribute to improved kidney health and better patient outcomes.

Conclusion

In summary, our systematic review and meta-analysis did not find statistically significant evidence supporting the overall efficacy of omega-3 fatty acids in reducing proteinuria across various kidney-related conditions. However, the complexity of this field, marked by diverse patient populations and intervention approaches, suggests that individual responses to omega-3 supplementation may vary. These results emphasize the need for targeted research to identify specific subgroups or conditions that may benefit from omega-3 fatty acid interventions. While our findings do not provide a definitive conclusion, they contribute to the evolving understanding of omega-3 fatty acids' potential role in personalized kidney health strategies, paving the way for further exploration and optimization of their therapeutic applications.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

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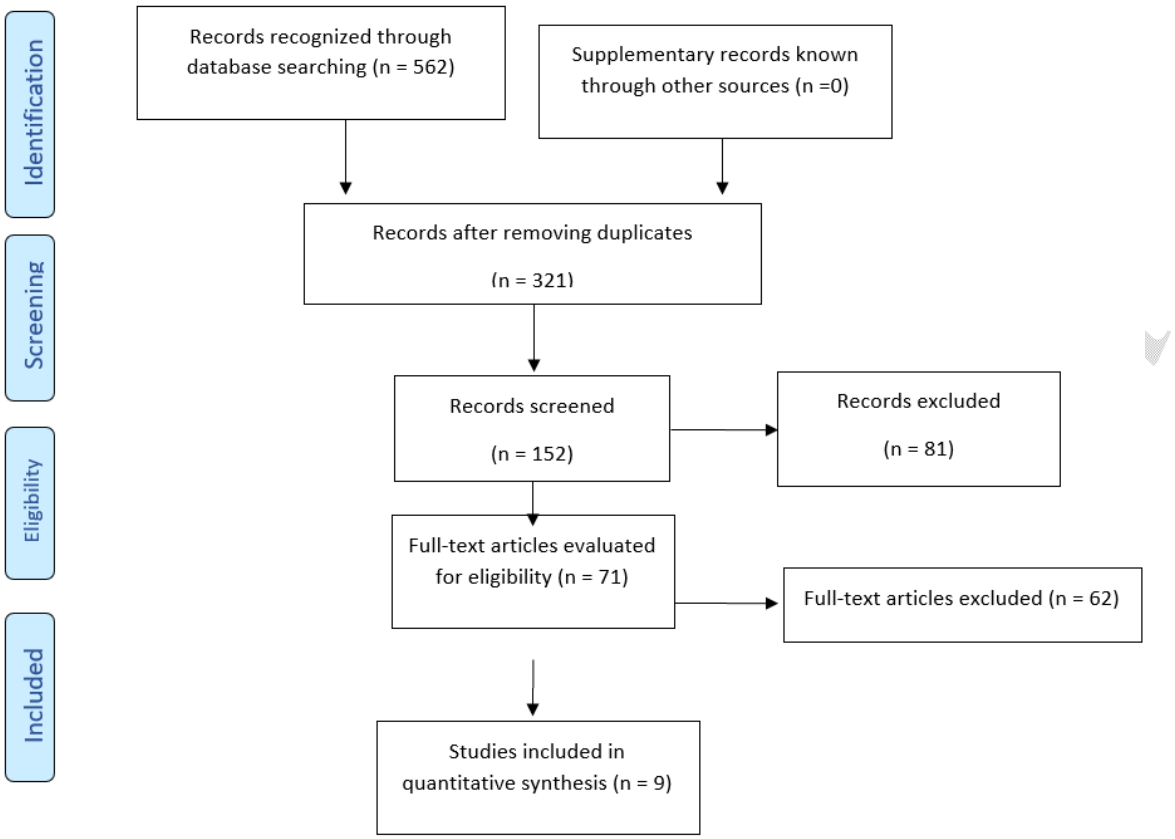
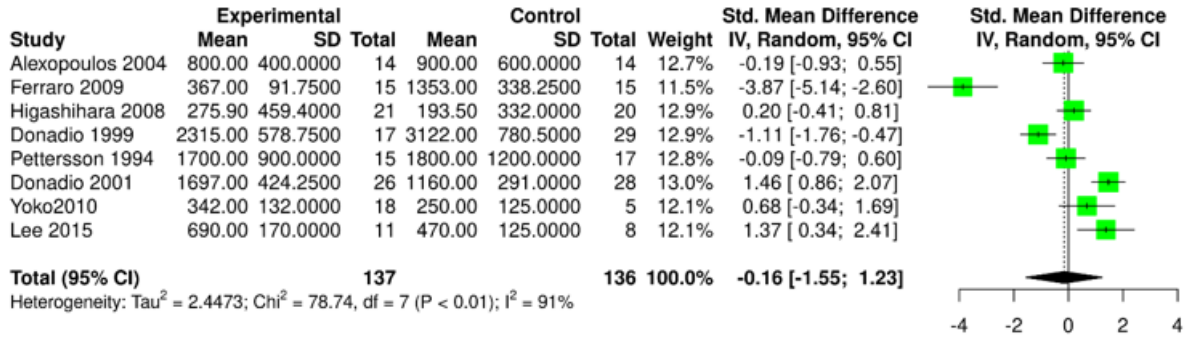


Figure 1. PRISMA flow diagram for the investigated studies.



Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Alexopoulos 2004	800.00	400.0000	14	900.00	600.0000	14	12.7%	-0.19 [-0.93; 0.55]
Ferraro 2009	367.00	91.7500	15	1353.00	338.2500	15	11.5%	-3.87 [-5.14; -2.60]
Higashihara 2008	275.90	459.4000	21	193.50	332.0000	20	12.9%	0.20 [-0.41; 0.81]
Donadio 1999	2315.00	578.7500	17	3122.00	780.5000	29	12.9%	-1.11 [-1.76; -0.47]
Pettersson 1994	1700.00	900.0000	15	1800.00	1200.0000	17	12.8%	-0.09 [-0.79; 0.60]
Donadio 2001	1697.00	424.2500	26	1160.00	291.0000	28	13.0%	1.46 [0.86; 2.07]
Yoko2010	342.00	132.0000	18	250.00	125.0000	5	12.1%	0.68 [-0.34; 1.69]
Lee 2015	690.00	170.0000	11	470.00	125.0000	8	12.1%	1.37 [0.34; 2.41]
Total (95% CI)			**137**			**136**	**100.0%**	**-0.16 [-1.55; 1.23]**

Heterogeneity: $Tau^2 = 2.4473$; $Chi^2 = 78.74$, df = 7 (P < 0.01); $I^2 = 91\%$

Figure 2. Forest plot for proteinuria meta-analysis.

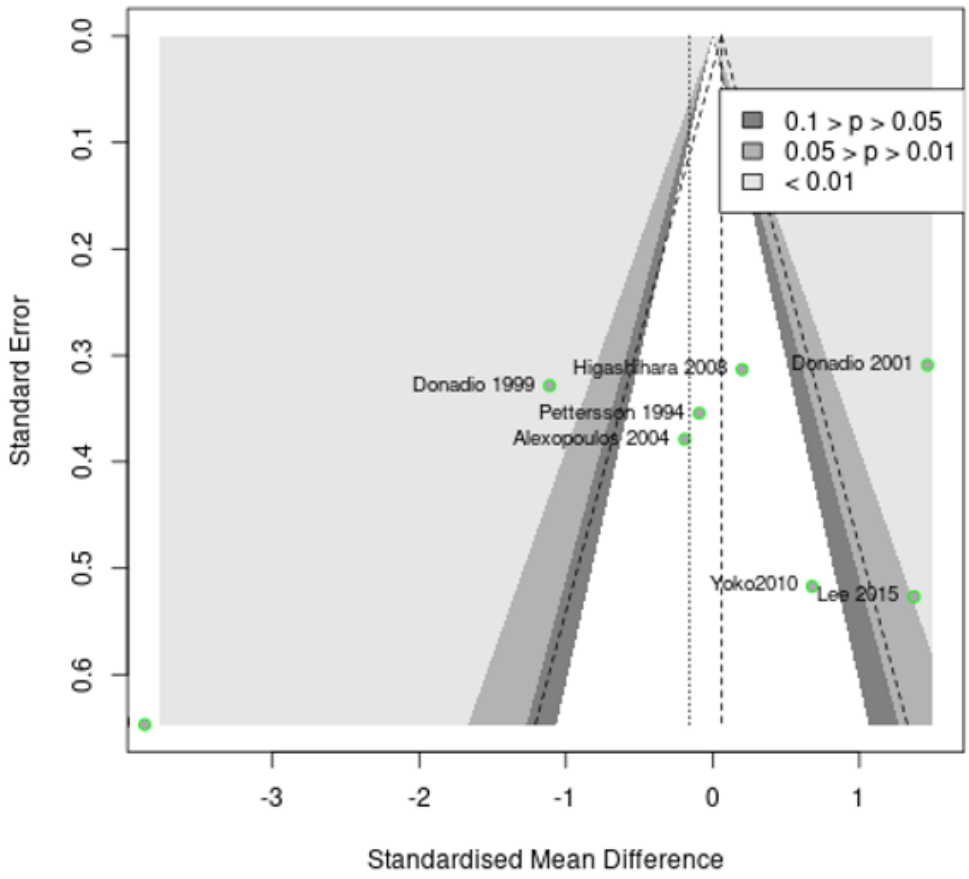


Figure 3. Funnel plot for meta-analysis of the studies.

Table 1. The key characteristics of the included studies

Study	Publication year	Country	Sample Size	Intervention
Alexopoulos E[16]	2004	Greece	14/14	EPA and PHA 5 g/d
Ferraro PM[17]	2009	Italy	15/15	RASB + PUFA 3.0 g/d
Higashihara E[18]	2008	Japan	21/20	2.4 g/day of EPA
Donadio JR[19]	1999	USA	17/29	daily dose of 12 g of fish oil
Pettersson EE[20]	1994	Sweden	15/17	PUFA (5.1 g/day)
Donadio JV[21]	2001	USA	26/28	2.94 g/d EPA and DHA
Bennett WM[22]	1989	Australia	18/19	EPA 10 g/d
Mori TA[23]	2009	Australia	19/18	Omega-3 capsules 4 g/d
Yoko UT[24]	2010	Japan	18/5	EPA 1.8 g/d plus ACEI/ARB
Lee SM[25]	2015	Korea	11/8	EPA 1.38 g/d

Study	Control	Disease status	JADAD* score	Duration
Alexopoulos E[16]	supportive treatment	IgA nephropathy	3	4 years
Ferraro PM[17]	RASB alone	IgA nephropathy	3	6 months
Higashihara E[18]	No treatment	ADPKD	3	24 months
Donadio JR[19]	placebo	IgA nephropathy	4	2 years
Pettersson EE[20]	placebo	IgA nephropathy	3	6 months
Donadio JV[21]	1.47 g/d EPA and DHA	IgA nephropathy	4	24 months
Bennett WM[22]	No treatment	IgA nephropathy	4	24 months
Mori TA[23]	Olive oil 4.0 g/d	CKD	4	2 months
Yoko UT[24]	ACEI/ARB	IgA nephropathy	2	12 months
Lee SM[25]	Olive oil	Diabetic nephropathy	3	3 months