Effect of omega-3 polyunsaturated fatty acids on left ventricular remodeling in chronic heart failure: a systematic review and meta-analysis

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Highlights of this study:
1. We provided a systematic and updated evaluation of ω-3 PUFAs supplementation on LV remodeling in patients with CHF.
2. The benefits of ω-3 PUFAs mediated LVEF improvement became more prominent when the accumulated dosage reached 600g.
3. ω-3 PUFAs supplementation reduced the levels of pro-inflammatory mediators including TNF-α, IL-6 and Hs-CRP.
Abstract:
Accumulating evidence suggests that supplementation of omega-3 polyunsaturated fatty acids (ω-3 PUFAs) was associated with reduction in risk of major cardiovascular events. This meta-analysis was to systematically evaluate whether daily supplementation and accumulated intake of ω-3 PUFAs is associated with improved left ventricular (LV) remodeling in patients with chronic heart failure (CHF). Articles were obtained from Pubmed, Clinical key and Web of Science from inception to January 1 in 2021, and a total of 12 trials involving 2162 participants were eligible for inclusion. The sources of study heterogeneity were explained by I² statistic and subgroup analysis. Compared with placebo groups, ω-3 PUFAs supplementation improved LV ejection fraction (LVEF) (11 trials, 2112 participants, WMD=2.52, 95%CI 1.25 to 3.80, I²=87.8%) and decreased LV end-systolic volume (LVESV) (5 studies, 905 participants, WMD=-3.22, 95%CI -3.67 to -2.77, I²=0.0%) by using the continuous variables analysis. Notably, the high accumulated ω-3 PUFAs dosage groups (≥600g) presented a prominent improvement in LVEF, while the low and middle accumulated dosage (≤300g and 300-600g) showed no effects on LVEF. In addition, ω-3 PUFAs supplementation decreased the levels of pro-inflammatory mediators including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and hypersensitive-c-reactive protein (Hs-CRP). Therefore, the present meta-analysis demonstrated that ω-3 PUFAs consumption was associated with a substantial improvement of LV function and remodeling in patients subjected to CHF. The accumulated dosage of ω-3 PUFAs intake is vital for its cardiac protective role.

Keywords: omega-3 polyunsaturated fatty acids; chronic heart failure; left ventricular remodeling; systematic review; meta-analysis
Introduction

Chronic Heart failure (CHF) is a clinical syndrome characterized by insufficient cardiac function, representing one of the largest contributors to mortality worldwide. The development of CHF arises from a molecular, and cellular transformation termed “ventricular remodeling”, which is featured by geometrical changes in the overall left ventricular (LV) shape and depression of LV ejection fraction (LVEF) (1). Ventricular remodeling is the main pathological basis of the occurrence and development of CHF, and is a decisive factor affecting the morbidity and mortality of CHF. HF patients can be categorized by LVEF (including HF with reduced EF (HFrEF), HF with preserved EF (HFpEF), HF with borderline EF (HFbEF)), and approximately 50% of cases are HFrEF (2).

Chronic inflammation is a key process in the pathophysiology of CHF. A number of pro-inflammatory cytokines have been implicated in the pathogenesis of HF including tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-1β (IL-1β), IL-6, IL-17, and IL-18 (3). For example, increasing circulating levels of TNF-α and IL-6 can weaken LV function and promote LV remodeling in a multicenter clinical trial of HF patients (4). A research have showed the negative inotropic effect of IL-1β, and currently IL-1β blocking agents are applied to treat HF states (5). Although current treatments can improve the syndrome to some extent, CHF remains a worsening global problem especially in ageing populations (6). Therefore, it is vital to explore effective prevention to block or slow down the progression of CHF despite the standard pharmacological.

Recommendations for the use of ω-3 PUFAs supplementation are included in several guidelines for the prevention of coronary heart disease (CHD) (7; 8; 9). Previous epidemiological researches found that supplementation of ω-3 PUFAs may prevent the development and progression of CHF (10; 11). A study showed that inflammatory cytokines (TNF-α, IL-1β) can reduce cardiac function and increase cardiac fibrosis to advance cardiac remodeling of HF patients (12), and ω-3 PUFAs reduced the levels of inflammation factors to prevent abnormal LV remodeling. In the GISSI-HF trial, 1g daily ω-3 PUFAs therapy provided a small but statistically significant improvement in LVEF, and further reduced the
mortality of HF by 9% after 3.9 years follow-up \(^{(13; 14)}\). A meta-analysis performed in 2012 demonstrated that fish oil increased the LV systolic function rather than diastolic function in non-ischemic HF patients \(^{(15)}\). The OMEGA-REMODEL trial suggested that dietary supplementation of high-dose \(\omega-3\) PUFAs reduced LV remodeling and inflammatory biomarkers \(^{(16)}\). However, other clinical trials reported that \(\omega-3\) PUFAs supplementation provides less beneficial cardiovascular outcomes on patients \(^{(17; 18; 19)}\). For example, researchers failed to find a protective effect for fish intake in the prevention of HF in the population-based Rotterdam Study \(^{(20)}\). Thus, the current meta-analysis aimed to provide a systematic and updated evaluation of \(\omega-3\) PUFAs supplementation on LV remodeling in patients with CHF.

**Methods**

We implemented a systematic review and meta-analysis according to the Quality of Reporting of Meta-analyses (QUOROM) guidelines in all stages \(^{(21)}\). The protocol of our study was registered in the PROSPERO database: CRD42020154553.

**Literature search strategy and selection criteria**

We performed a search through Pubmed, Clinical key and Web of Science up to January 1 in 2021 and the search terms were (Omega-3 OR Omega-3 fatty acids OR n-3 Fatty Acids OR n-3 Polyunsaturated Fatty Acid OR n-3 PUFA OR n-3 Oils) AND (cardiac function or heart function) AND (clinical trials). J.L and Q.S.M independently screened all eligible citations including titles, abstracts, and full texts and references when necessary.

Eligible studies were included as the following criteria: (a) non-repetitive clinical trials of \(\omega-3\) PUFAs supplementation (both dietary supplements and capsules of \(\omega-3\)); (b) participants were patients who were diagnosed as CHF; (c) provided information about cardiac function; (d) English language publications.

**Date extraction**

We extracted the following data from each of the included studies: the first author, the journal, publication year, country, age, male number of participants, aetiology of patients (dilated cardiomyopathy (DCM), ischemic cardiomyopathy (ICM), ICM/DCM), body mass
index (BMI), daily dosage of ω-3 PUFAs, duration, total dosages of ω-3 PUFAs, the original values at baseline and the end of the trials including LVEF, LV end systolic volume/diameter (LVESV/LVESD), LV end diastolic volume/diameter (LVEDV/LVEDD), and circulating inflammatory mediators including TNF-α, IL-6 and hypersensitive c-reactive protein (Hs-CRP) (mean ± SD). Total dosages were calculated as (daily dosage) × (total number of days at the time of examination) (one month was equivalent to 30 days). The outcomes were assessed by the changes in LVEF, LVESV, LVEDV, LVESD, LVEDD, TNF-α, IL-6 and Hs-CRP, from the baseline to the end of intervention. The SD changes of outcomes were calculated by averaging the placebo SD and ω-3 PUFAs intervention SD. For the left ventricular remodeling indices, including LVEF, LVESV, LVEDV, LVESD, LVEDD, TNF-α, IL-6 and Hs-CRP, most of the literature provided the means ± SD at baseline and the end of the intervention. However, some studies only reported variables in the form of median and interquartile range. In such case, means and SD were converted with the information of median, interquartile range and sample size using an estimation method published by Hozo and colleagues. In Hozo’s paper, the median itself is the best estimator for mean when the sample size exceeds 25, which is the case for the included studies in our paper. And the SD was estimated using the formula: 1) 15<sample size≤70, SD=(Max-Min)/4; 2) sample size>70, SD=(Max-Min)/6.

Quality assessment of included studies

The quality of all included randomized controlled trials (RCTs) (10 trials) was assessed by authors using the Cochrane Collaboration’s Tool and the Revised JADAD’s Scale. On the Cochrane Collaboration’s Tool, seven specific aspects were addressed and the judgement was expressed by low, unclear and high. The Revised JADAD’s Scale assessed the risk of bias and scored by 0, 1 and 2. Additionally, the Newcastle-Ottawa Scale analyzed and scored the prospective studies.
Statistical analyses

The primary study outcomes were assessed by the changes of left ventricular remodeling indices including LVEF, LVESV, LVEDV, LVESD, LVEDD, and circulating inflammatory mediators including TNF-α, IL-6 and Hs-CRP in both ω-3 PUFAs treated and placebo groups, from the baseline to the end of intervention. All statistical analyses were conducted using the statistical software STATA software, version 12.0 (StataCorp LP, College Station, TX). For the continuous variables, the pooled effects were presented as weighted mean difference (WMD) with 95% confidence interval (CI). \( I^2 \) test was used to evaluate the clinical heterogeneity, and \( I^2 \geq 50\% \) indicated obvious heterogeneity \(^{(24)}\). The random-effects model was used to assess the pooled data considering both intra and interstudy variations. A forest plot was conducted to show the relationship between ω-3 PUFAs and LV remodeling indices. Sensitivity analysis was performed to determine the reliability of the data by sequentially eliminating each of the included studies. Publication bias was measured using a Begg and Egger regression asymmetry test.

Results

Selection of Studies

The search strategy resulted in 777 articles for consideration in the present meta-analysis. After removing duplicated 80 records, the titles and abstracts of the remaining 697 records were further examined, and 640 records were excluded based on the inclusion criteria. A full text examination was performed in the remaining 57 studies and 12 studies were eligible for the current analysis based on the selection criteria, of which 10 studies were RCTs \(^{(4; 14; 16; 22; 25; 26; 27; 28; 29; 30)}\), and 2 studies were prospective studies \(^{(31; 32)}\). The flow diagram of the initial literature search and trial selection was shown in Figure 1.

Baseline Characteristics

Baseline characteristics of included trials are summarized in Table 1. A total of 2162 participants were included, with age (years) range from 55.1 to 74.0. The 12 trials were variously performed in the eastern (China \(^{(27)}\), Iran \(^{(30)}\), Japan \(^{(31)}\)) and the western (Denmark \(^{(25)}\), Italy \(^{(14; 26; 28; 29)}\), Austria \(^{(4)}\), USA \(^{(16)}\), Brazil \(^{(32)}\), Greece \(^{(22)}\)) countries. Baseline and
follow-up LVEF scores were available in 11 studies. In the 11 clinical trials, 9 studies were diagnosed as HFrEF (LVEF≤40%) \(^{(4; 14; 22; 26; 27; 28; 29; 30; 31)}\), whereas 2 studies were diagnosed as HFpEF (LVEF≥50%) \(^{(16; 32)}\). Changes in LVESV \(^{(14; 25; 28; 29; 30)}\) and LVEDD \(^{(14; 22; 27; 29; 30)}\) were available in 5 trials. LVEDV \(^{(14; 25; 29; 32)}\) and LVESD \(^{(22; 27; 29; 30)}\) data were evaluated in 4 studies. TNF-α \(^{(4; 27; 28; 29; 31)}\), IL-6 \(^{(4; 27; 28; 29)}\) and Hs-CRP \(^{(4; 27; 31; 32)}\) were evaluated from data extracted from 5, 4, 4 studies, respectively. 11 trials (1804 participants) assessed cardiac function using echocardiography while 1 study (358 participants) \(^{(16)}\) used cardiac Magnetic Resonance Imaging (cMRI). The aetiology of CHF participants was classified as ICM in 4 studies \(^{(16; 26; 30; 32)}\), DCM in 3 studies \(^{(4; 28; 29)}\) and both ICM and DCM in 4 studies \(^{(14; 22; 27; 31)}\), respectively.

**Administration details of ω-3 PUFAs and placebo groups**

In all included studies, the daily dosage of ω-3 PUFAs varied from 1g/d to 5.2g/d, with duration ranged from 3 months to 12 months. The daily dosage of EPA ranged between 360 to 1860 mg and DHA ranged from 240 to 1500 mg, compared with a recommended dietary intake of 250 to 2000 mg/d for each \(^{(33)}\). 11 trials evaluated the combined effect of ω-3 PUFAs supplementation \(^{(4; 14; 16; 22; 25; 26; 27; 28; 29; 30; 32)}\) while 1 trial assessed independent effect of EPA \(^{(31)}\). The placebo composition included olive oil \(^{(25; 28; 29)}\), linoleic acid \(^{(16)}\) or no pills \(^{(22)}\). The supplements of placebo groups were not mentioned in the remaining 7 studies \(^{(4; 14; 26; 27; 30; 31; 32)}\).

**Study quality assessment**

The quality assessment of RCTs was analyzed by Cochrane Collaboration’s Tool and generally of good quality (Supplementary figure 1). In the Revised JADAD’s Scale, 4 studies scored 4 \(^{(25; 26; 27; 28)}\), 4 studies scored 5 \(^{(14; 22; 29; 30)}\) and the other 2 studies scored 7 \(^{(4; 16)}\) (Supplementary table 1A). The 2 prospective studies were assessed by the Newcastle-Ottawa Scale and the result showed 1 study scored 7 \(^{(31)}\) while the other scored 6 \(^{(32)}\) (Supplementary table 1B).
Effects of ω-3 PUFAs supplementation on ventricular remodeling

Compared to placebo groups, ω-3 PUFAs supplementation improved LVEF by a WMD of 2.52 (95% CI 1.25 to 3.80, 𝐈²=87.8%, Figure 2A). Additionally, ω-3 PUFAs supplementation significantly decreased LVESV (WMD=-3.22, 95% CI -3.67 to -2.77, 𝐈²=0.0%, Figure 2B). The pooled results indicated that the differences were not statistically significant for LVEDV (Figure 2C), LVESD (Figure 2D) or LVEDD (Figure 2E). The 𝐈² value for studies assessing LVEF changes was 87.8%, indicating a significant heterogeneity across the studies.

Next, the subgroup analysis was conducted to explore the sources of the heterogeneity (Table 2). In American College of Cardiology and American Heart Association guidelines, HF patients can be categorized by LVEF, including HFpEF (LVEF ≥50%), HFrEF (LVEF 41% to 49%) and HFrEF (LVEF ≤40%) (2). In the current study, LVEF improved by 2.02% in HFrEF patients taking ω-3 PUFAs (WMD=2.02, 95% CI 0.70 to 3.34, 𝐈²=87.0%), while it increased by 4.59% in HFpEF group (WMD=4.59, 95% CI 0.87 to 8.31, 𝐈²=78.1%). In the aetiology subgroup, the LVEF was prominently increased in DCM patients (WMD=4.49, 95% CI 2.72 to 6.26, 𝐈²=0.0%), while no significant improvement could be observed in the ICM and ICM/DCM subgroups. Subgrouping according by BMI showed no significant improvement in LVEF in either normal weight patients (BMI=18.5-24.9 kg/m²) or pre-obesity patients (BMI=25.0-29.9 kg/m²). Based on the regions, results from studies in the western countries revealed a significant association between improvement in LVEF and ω-3 PUFAs intake (WMD=2.19, 95% CI 0.92 to 3.47, 𝐈²=86.8%).

Dosage accumulation effect of ω-3 PUFAs on LVEF improvement

Further subgroup analysis was performed to examine whether the efficacy on LVEF was associated with the dosage of ω-3 PUFAs supplementation (Table 2). Average daily dosage, duration and total dosages for all included studies were summarized in Table 1. Subgrouping according by average daily intake showed ω-3 PUFAs at a dosage of 1-3g/d (WMD=3.60, 95% CI 0.86 to 6.33, 𝐈²=87.5%) and ≥3g/d (WMD=2.96, 95% CI 1.25 to 3.80, 𝐈²=0.0%) had beneficial effects in LVEF, whereas ≤1g/d showed no significant improvement.
Duration seemed to have effects on LVEF improvement, as a trend favored a longer ω-3 PUFAs duration with a better LVEF improvement. Although short duration (≤6 months) had no significant effects on LVEF scores, the improvement was significant in long duration (>6 months) (WMD=4.53, 95%CI 0.02 to 3.80, $I^2=95.2\%$) intervention subgroup. Of note, subgroup analysis according to total ω-3 PUFAs intake showed a dosage-dependent accumulation effect on LVEF improvement: there were no significant improvement in LVEF at a dosage of ≤300g and a high dosage 300-600g, while a much higher dosage (≥600g) achieved a greater benefit in LVEF scores (WMD=5.23, 95%CI 2.31 to 8.15, $I^2=77.1\%$).

**Effects of ω-3 PUFAs intake on circulating inflammatory mediators**

Increased secretion of circulating inflammatory mediators were associated with the pathogenesis and progression for cardiac mortality and ventricular remodeling (34; 35). Results showed that both TNF-α (WMD=-3.48, 95%CI -4.67 to -2.30, $I^2=97.9\%$, Figure 3A) and IL-6 (WMD=-3.85, 95%CI -6.05 to -1.64, $I^2=94.2\%$, Figure 3B) levels significantly decreased in ω-3 PUFAs treated group compared to placebo groups. Hs-CRP was also decreased in ω-3 PUFAs treated group (WMD=-0.23, 95%CI -0.41 to -0.05, $I^2=80.8\%$, Figure 3C).

**Publication bias and sensitivity analysis**

As shown in the funnel plot, there was no publication bias in the effects of ω-3 PUFAs on LVEF (Figure 4). Sensitivity analysis showed that none of the studies changed the overall effect of ω-3 PUFAs supplements on LVEF improvements.
Discussion

This meta-analysis of 12 studies had several findings: First, ω-3 PUFAs treatment contributed to improve the LVEF and LVESV. Second, the benefits of ω-3 PUFAs mediated LVEF improvement seemed to be dependent on the accumulated dosage, which reflects combined effects of daily intake and duration. The benefits became more prominent when the accumulated dosage reached 600g. Third, ω-3 PUFAs supplementation reduced the levels of circulating TNF-α, IL-6 and Hs-CRP. Collectively, these results supported that ω-3 PUFAs supplementation had a positive association with cardiac function and support its current recommendation in CHF patients (36).

LV remodeling is generally accepted as a critical factor in the progression of CHF. During the process of ventricular remodeling, structural and functional changes can be evaluated by a series of image examinations (37), among which, echocardiography and cMRI are most frequently used (38). Compared with echocardiography, cMRI displays a better performance in cardiac remodeling assessment due to its clear contrast resolution and high reproducibility (39). However, only one study used cMRI in the current study, which demonstrated that ω-3 PUFAs significantly inhibited the LVESV index and myocardial fibrosis (16). Further large-scale studies using cMRI are needed to evaluate the effect of ω-3 PUFAs on cardiac remodeling.

ω-3 PUFAs, have attracted interest as a possible addition to available lifestyle measures and medications for the prevention of cardiovascular diseases (40). Previous study showed the cardioprotective mechanisms of ω-3 PUFAs against HF, including anti-inflammatory; intervention of cardiac energy metabolism; modification of cardiac ion channels; improvement of vascular endothelial; modulation of autonomic nervous system activity (41, 42, 43). The American Heart Association advisory board recommended ω-3 PUFAs supplementation (1g/d, 2 years) in CHF patients for the secondary prevention of cardiovascular disease death (36). Meanwhile, several animal studies provide solid evidence that ω-3 PUFAs supplementation not only prevent diastolic and systolic dysfunction but also improve abnormal ventricular remodeling (44, 45). A previous meta-analysis performed in
2012 indicated ω-3 PUFAs supplementation of CHF patients led to a significantly increase in LVEF and a reduction in LVESV (15), while a recent meta-analysis performed in 2016 produced inconsistent conclusions (46). The current study provided an updated analysis about the effects of ω-3 PUFAs in CHF patients, and suggested that ω-3 PUFAs supplementation could lead to improvement in LVEF and reduction in LVESV.

Additionally, our results showed the recovery of LVEF by ω-3 PUFAs supplementation in both HFpEF and HFrEF patients. Though HFpEF subgroup is relatively small (2 trials), the LVEF improvement was evident. As a disease with limited evidence-based treatment options, our data support the application of ω-3 PUFAs supplementation in HFpEF patients. For HFrEF patients suffering from a progressive LVEF decay, ω-3 PUFAs supplementation could help to preserve LVEF level with slight but significant improvements. Furthermore, recent research showed that ω-3 PUFAs may determine long-term change in weight and the high dosage of ω-3 PUFAs intake can alleviate the genetic associations with changes in BMI (47). However, no remarkable improvement in LVEF was found in either normal weight patients or pre-obesity patients in our study. Apart from the above discussed factors, there seemed to be regional disparity in ω-3 PUFAs mediated LVEF improvements. Dietary patterns in different regions might partly explain the disparity. Limited access to marine fish, which is the main dietary source of ω-3 PUFAs, might contribute to a severe deficiency of ω-3 PUFAs (48). Hence, we considered that different dietary intake might contribute to the conflicting results between the western and the eastern countries. Especially, the Japan, which had large fish consumption (31), showed a favorable trend on LVEF in eastern subgroup.

ω-3 PUFAs can have a broad range of effects on inflammation, oxidation, and stability of phospholipid membranes (49). The American and European guidelines have stated that prescription of ω-3 PUFAs (EPA + DHA or EPA-only) at a dose of 4 g/d is an effective and safe option for reducing triglycerides as monotherapy or as an adjunct to other lipid-lowering agents (50; 51). However, clinical trials reported inconsistent benefits from ω-3 PUFAs on cardiovascular events, even in trials using the same high dose of ω-3 PUFAs.
(4g/d) (52; 53). A proper dosage has been raised as one of the possible reasons for the contradictory results (54; 55). The improvement in adverse LV remodeling during infarct convalescence remains the strongest favorable risk predictor, and serves as a common mechanistic pathway that reduces mortality, sudden cardiac death, and heart failure incidence (56). However, the cardiac remodeling is a long-term process and its improvement might be vague within short-term observation period, especially for the patients who received standard medical care of CHD. Our data suggested a longer intervention period of ω-3 PUFAs correlated with a favorable effect on LVEF. Additionally, it should be noted that the 2 included studies in the ≥3g/d subgroup had a relative short duration (3-6 months), while 5 out of 7 included studies in the 1-3g/d subgroup had a longer duration (6-12 months). As both daily dose and duration might be influencing factors for the effects of ω-3 PUFAs, we speculated that the accumulated dosage, indicative for the two factors, might serve as a comprehensive parameter to evaluate the effects of ω-3 PUFAs. Though the included trials were limited, our data suggested that a sufficient accumulated dosage (≥600g) was essential for ω-3 PUFAs mediated LVEF improvements (Table 2).

But, the high heterogeneity was the major challenge to clarify the associations of ω-3 PUFAs supplementation with LVEF improvements. We conducted meta-regression, sensitivity and subgroup analysis to identify potential sources of heterogeneity. The meta-regression and sensitivity analysis could not reduce the heterogeneity. Subgroup analyses revealed that several variables contributed to the heterogeneity of this meta-analysis including LVEF classification, aetiology, daily intake, duration and accumulated dosages.

Apart from structural and functional changes, evidences had shown that inflammatory response played an important role in ventricular remodeling (57). The induction of cytokines (such as IL-6, TNF-α) may be involved in the pathogenesis of adverse remodeling, cardiac dysfunction, and ultimately HF. Persistent dysregulated inflammation response might induce cardiac hypertrophy, damage myocardial contractility and finally contribute to LV remodeling (58). Clinically, patients with higher degrees of inflammation, as measured by
circulating N-terminal-pro-type B natriuretic peptide (BNP) and Hs-CRP, had increased morbidity and mortality \(^{(59)}\). Daily intake of \(\omega-3\) PUFAs could attenuate inflammatory response, which further prevent the progression of HF or ST-elevation MI patients \(^{(27;32;60)}\). In HF patients, the pro-inflammatory cytokines were activated by nuclear transcription factor kappa B which was suppressed by \(\omega-3\) PUFAs, as evidenced by a reduced the circulating level of TNF-\(\alpha\), IL-1 and IL-6 \(^{(61)}\). In a rat model of MI, increasing expression of IL-6, TNF-\(\alpha\) and IL-1 in myocardium were significantly associated with increased LVEDD \(^{(62)}\). Our results suggested that \(\omega-3\) PUFAs supplementation significantly reduced the expression of inflammation cytokines including TNF-\(\alpha\), IL-6 and Hs-CRP. These effects might explain how \(\omega-3\) PUFAs supplementation attenuated the cardiac remodeling.

**Limitation**

Our study had some potential limitations. First, due to limited trials, the heterogeneity of LVEF scores remained significant even after stratification by the LVEF classification, aetiology, BMI and regions. Second, these were no reports about the effect of \(\omega-3\) PUFAs on patients with HFbIEF yet, so the present meta-analysis could not give any evidence on \(\omega-3\) PUFAs supplementation in this population. Third, other measurements and circulating inflammatory mediators such as left atrial volumes and NT-pro-BNP might possibly link to ventricular remodeling and need further investigation.

**Conclusion**

This meta-analysis demonstrated that \(\omega-3\) PUFAs supplementation was associated with a substantial improvement of LV function and remodeling in patients subjected to CHF. \(\omega-3\) PUFAs intake also decreased the levels of circulating pro-inflammatory factors in CHF patients. The accumulated dosage of \(\omega-3\) PUFAs consumption is vital for its cardiac protective role.
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Authors’ contribution

The authors’ contributions were as follows. XZ and XL contributed to the conception and design of the study. JL, QM, LZ, PY, HH, RZ, XG, ZL contributed to acquisition, analysis and interpretation of the data. JL wrote the MS. QM, LZ, PY, HH, RZ, XG, ZL, XL and XZ revised the MS. All authors read and approved the final manuscript.

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Figure 1: Flow diagram of the systematic review and meta-analysis.
Accepted manuscript

Figure 2A

Figure 2B

Figure 2C
Figure 2: Forest plot indicated the effects of ω-3 PUFAs supplementation on cardiac function. (A) Effect of ω-3 PUFAs supplementation on LVEF. (B-E) Effect of ω-3 PUFAs supplementation on LVESV, LVEDV, LVESD and LVEDD. I² indicated the degree of studies heterogeneity; CI, confidence interval; WMD, weighed mean difference; LVEF, left ventricular ejection fraction; LVESV/LVESD, left ventricular end systolic volume/diameter; LVEDV/LVEDD, left ventricular end diastolic volume/diameter.
Figure 3A

Figure 3B
Figure 3: Forest plot of the effect of ω-3 PUFAs on inflammatory cytokines. (A) The effect of ω-3 PUFAs on TNF-α. (B) The effect of ω-3 PUFAs on IL-6. (C) The effect of ω-3 PUFAs on Hs-CRP. TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; Hs-CRP, hyper sensitive c-reactive protein.
Figure 4: Funnel plot of the effect of ω-3 PUFAs on LVEF.
Supplementary figure 1: The RCTs were assessed by using the Cochrane Collaboration’s Tool. Green represented low risk of bias, yellow represented unclear, red represented high risk of bias.
Table 1: Baseline characteristics of included trials are summarized.

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<th>Authors</th>
<th>Country</th>
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<td>3</td>
<td>180</td>
<td>24.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>placebo</td>
<td>71</td>
<td>10</td>
<td>28(76)</td>
<td></td>
<td></td>
<td></td>
<td>24.0</td>
</tr>
<tr>
<td>Nodari S et al. (2009)</td>
<td>Italy</td>
<td>ω-3 PUFAs</td>
<td>61.09</td>
<td>11.22</td>
<td>21(95.4)</td>
<td>5g/d-1 months; 1g/d-5 months</td>
<td>6</td>
<td>300</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>placebo</td>
<td>64.82</td>
<td>9.46</td>
<td>19(86.4)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ghio S et al. (2010)</td>
<td>Italy</td>
<td>ω-3 PUFAs</td>
<td>65</td>
<td>10</td>
<td>274(87.8)</td>
<td>1</td>
<td>12</td>
<td>360</td>
<td>25.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>placebo</td>
<td>65</td>
<td>11</td>
<td>238(80.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodari S et al. (2011)</td>
<td>Italy</td>
<td>ω-3 PUFAs</td>
<td>61</td>
<td>11</td>
<td>64(95.5)</td>
<td>5g/d-1 month; 2g/d-11 month</td>
<td>12</td>
<td>810</td>
<td>25.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>placebo</td>
<td>64</td>
<td>9</td>
<td>56(84.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moertl D et al. (2011)</td>
<td>Austria</td>
<td>ω-3 PUFAs</td>
<td>58.6</td>
<td>7.0</td>
<td>12(86)</td>
<td>1</td>
<td>3</td>
<td>90</td>
<td>27.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ω-3</td>
<td>61.9</td>
<td>9.6</td>
<td>13(100)</td>
<td></td>
<td></td>
<td>4</td>
<td>360</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>ω-3 PUFAs Placebo</td>
<td>ω-3 PUFAs</td>
<td>BMI (kg/m²)</td>
<td>DCM</td>
<td>ICM</td>
<td>N/A</td>
<td>ICN</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------</td>
<td>--------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-----</td>
<td>-----</td>
<td>-------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>Kojuri et al. (2013)</td>
<td>Iran</td>
<td>55.1</td>
<td>12.7</td>
<td>12(75)</td>
<td>N/A</td>
<td>N/A</td>
<td>28.0</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Kohashi K et al. (2014)</td>
<td>Japan</td>
<td>56</td>
<td>N/A</td>
<td>22(58)</td>
<td>2</td>
<td>6</td>
<td>360</td>
<td>ICM/N/A</td>
<td></td>
</tr>
<tr>
<td>Heydari B et al. (2016)</td>
<td>USA</td>
<td>60</td>
<td>10</td>
<td>148(82)</td>
<td>1.8</td>
<td>12</td>
<td>648</td>
<td>ICM/DCM</td>
<td></td>
</tr>
<tr>
<td>Chrysohoou C et al. (2016)</td>
<td>Greece</td>
<td>63</td>
<td>12.8</td>
<td>80(79.2)</td>
<td>4</td>
<td>6</td>
<td>720</td>
<td>ICM</td>
<td></td>
</tr>
<tr>
<td>Campos-Staffico AM et al. (2019)</td>
<td>Brazil</td>
<td>58</td>
<td>11</td>
<td>165(76)</td>
<td>≥1.7</td>
<td>6</td>
<td>≥306</td>
<td>ICM</td>
<td></td>
</tr>
</tbody>
</table>

ω-3 PUFAs: omega-3 polyunsaturated fatty acids; BMI: Body mass index; DCM: dilated cardiomyopathy; ICM: ischemic cardiomyopathy; N/A: not applicable.
Table 2: Subgroup analysis of ω-3 PUFAs in CHF patients

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Studies</th>
<th>Overall effect</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>n:references</td>
<td>WMD(95%CI)</td>
<td>I², %</td>
</tr>
<tr>
<td>≤40%</td>
<td>9: Ghio S et al. (2010); Chrysohoou C et al. (2016); Radaelli A et al. (2006); Zhao YT et al. (2009); Nodari S et al. (2011); Moertl D et al. (2011); Kojuri J et al. (2013); Kohashi K et al. (2014)</td>
<td>2.02(0.70,3.34)</td>
<td>87.0</td>
</tr>
<tr>
<td>≥50%</td>
<td>2: Heydari B et al. (2016); Campos-Staffico AM et al. (2019)</td>
<td>4.59(0.87,8.31)</td>
<td>78.1</td>
</tr>
<tr>
<td>Aetiology</td>
<td>n:references</td>
<td>WMD(95%CI)</td>
<td>I², %</td>
</tr>
<tr>
<td>ICM</td>
<td>4: Heydari B et al. (2016); Radaelli A et al. (2006); Kojuri J et al. (2013); Campos-Staffico AM et al. (2019)</td>
<td>2.27(-0.76,5.29)</td>
<td>85.4</td>
</tr>
<tr>
<td>ICM/DCM</td>
<td>4: Ghio S et al. (2010); Chrysohoou C et al. (2016); Zhao YT et al. (2009); Kohashi K et al. (2014)</td>
<td>1.84(-0.20,3.88)</td>
<td>94.1</td>
</tr>
<tr>
<td>DCM</td>
<td>3: Nodari S et al. (2009); Nodari S et al. (2011); Moertl D et al. (2011)</td>
<td>4.49(2.72,6.26)</td>
<td>0.0</td>
</tr>
<tr>
<td>BMI</td>
<td>n:references</td>
<td>WMD(95%CI)</td>
<td>I², %</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>2: Zhao YT et al. (2009); Kohashi K et al. (2014)</td>
<td>4.62(-2.34,11.58)</td>
<td>90.8</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>5: Heydari B et al. (2016); Chrysohoou C et al. (2016); Nodari S et al. (2011); Moertl D et al. (2011); Campos-Staffico AM et al. (2019)</td>
<td>3.15(-0.05,6.34)</td>
<td>91.3</td>
</tr>
<tr>
<td>Location</td>
<td>Western</td>
<td>Eastern</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Dosage of ω-3 PUFAs</td>
<td>≤1 g/d</td>
<td>1-3 g/d</td>
<td>≥3 g/d</td>
</tr>
<tr>
<td>Duration</td>
<td>&lt;6 months</td>
<td>=6 months</td>
<td>&gt;6 months</td>
</tr>
<tr>
<td>Location</td>
<td>Heydari B et al. (2016); Ghio S et al. (2010); Chrysohoou C et al. (2016); Radaelli A et al. (2006); Nodari S et al. (2009); Nodari S et al. (2011); Moertl D et al. (2011); Campos-Staffico AM et al. (2019)</td>
<td>Zhao YT et al. (2009); Kojuri J et al. (2013); Kohashi K et al. (2014)</td>
<td>Ghio S et al. (2010); Chrysohoou C et al. (2016); Moertl D et al. (2011)</td>
</tr>
<tr>
<td>WMD: weighted mean difference; ω-3 PUFAs: omega-3 polyunsaturated fatty acids; LVEF: left ventricular ejection fraction; BMI: Body mass index.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Supplementary table 1 (A): The RCTs were assessed using Revised JADAD’s Scale.

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence production</th>
<th>Allocation concealment</th>
<th>Blind method</th>
<th>Withdrawal</th>
<th>Total scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skou HA et al. (2001)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Radaelli A et al. (2006)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Zhao YT et al. (2009)</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Nodari S et al. (2009)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Ghio S et al. (2010)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Nodari S et al. (2011)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Moertl D et al. (2011)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Kojuri J et al. (2013)</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Chrysohoou C et al. (2016)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Heydari B et al. (2016)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>
Supplementary table 1 (B): The prospective studies were assessed by the Newcastle-Ottawa Scale.

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Exposure/Outcome</th>
<th>Total scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohashi K et al. (2014)</td>
<td>****</td>
<td>*</td>
<td>**</td>
<td>7</td>
</tr>
<tr>
<td>Campos-Staffico AM et al. (2019)</td>
<td>****</td>
<td>*</td>
<td>*</td>
<td>6</td>
</tr>
</tbody>
</table>