Effect of *n*-3 PUFA on left ventricular remodelling in chronic heart failure: a systematic review and meta-analysis

Jing Liu[1,2], Qingshu Meng[1,3,4], Liang Zheng[1,3,4], Ping Yu[5], Hao Hu[5], Rulin Zhuang[1,6], Xinyu Ge[1,6], Zhongmin Liu[1,4,6], Xiaoting Liang[1,3,4,7]* and Xiaohui Zhou[1,3,4]*

[1]*Research Center for Translational Medicine, Shanghai East Hospital, Tongji University School of Medicine, Shanghai 200120, People's Republic of China*

[2]*Department of Burn & Plastic Surgery, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, People's Republic of China*

[3]*Institute of Integrated Traditional Chinese and Western Medicine for Cardiovascular Chronic Diseases, Tongji University School of Medicine, Shanghai 200120, People's Republic of China*

[4]*Shanghai Heart Failure Research Center, Shanghai East Hospital, Tongji University School of Medicine, Shanghai 200120, People's Republic of China*

[5]*Department of Heart Failure, Shanghai East Hospital, Tongji University School of Medicine, Shanghai 200120, People's Republic of China*

[6]*Department of Cardiovascular Surgery, Shanghai East Hospital, Tongji University School of Medicine, Shanghai 200120, People's Republic of China*

[7]*Institute for Regenerative Medicine, Shanghai East Hospital, School of Life Sciences and Technology, Tongji University, Shanghai 200120, People's Republic of China*

Abstract

Accumulating evidence suggests that supplementation of *n*-3 PUFA was associated with reduction in risk of major cardiovascular events. This meta-analysis was to systematically evaluate whether daily supplementation and accumulated intake of *n*-3 PUFA are associated with improved left ventricular (LV) remodelling 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 twelve trials involving 2162 participants were eligible for inclusion. The sources of study heterogeneity were explained by I^2 statistic and subgroup analysis. Compared with placebo groups, *n*-3 PUFA supplementation improved LV ejection fraction (LVEF) (eleven trials, 2112 participants, weighted mean difference (WMD) = 2·52, 95 % CI 1·25, 3·80, I^2 = 87·8 %) and decreased LV end systolic volume (five studies, 905 participants, WMD = −3·22, 95 % CI 3·67, −2·77, I^2 = 0·0 %) using the continuous variables analysis. Notably, the high accumulated *n*-3 PUFA dosage groups (≥ 600 g) presented a prominent improvement in LVEF, while the low and middle accumulated dosage (≤ 300 and 300–600 g) showed no effects on LVEF. In addition, *n*-3 PUFA supplementation decreased the levels of pro-inflammatory mediators including TNF-α, IL-6 (IL-6) and hypersensitive c-reactive protein. Therefore, the present meta-analysis demonstrated that *n*-3 PUFA consumption was associated with a substantial improvement of LV function and remodelling in patients subjected to CHF. The accumulated dosage of *n*-3 PUFA intake is vital for its cardiac protective role.

Key words: ***n*-3 PUFA: Chronic heart failure: Left ventricular remodelling: Systematic review: meta-analysis**

Highlights of this study

We provided a systematic and updated evaluation of *n*-3 PUFA supplementation on LV remodelling in patients with CHF.

The benefits of *n*-3 PUFA mediated LVEF improvement became more prominent when the accumulated dosage reached 600 g.

n-3 PUFA supplementation reduced the levels of pro-inflammatory mediators including TNF-α, IL-6 and Hs-CRP.

Abbreviations: CHF, chronic heart failure; cMRI, cardiac MRI; DCM, dilated cardiomyopathy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; Hs-CRP, hypersensitive c-reactive protein; ICM, ischaemic cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; WMD, weighted mean difference.

* **Corresponding authors:** Xiaoting Liang, email liangxt@tongji.edu.cn; Xiaohui Zhou, email zxh100@tongji.edu.cn

Chronic heart failure (CHF) is a clinical syndrome characterised 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 remodelling', which is featured by geometrical changes in the overall left ventricular (LV) shape and depression of LV ejection fraction (LVEF)[1]. Ventricular remodelling is the main pathological basis of the occurrence and development of CHF and is a decisive factor affecting the morbidity and mortality of CHF. Heart failure (HF) patients can be categorised by LVEF (including HF with reduced ejection fraction (EF) (HFrEF), HF with preserved EF (HFpEF), HF with borderline EF), 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 TNF-α, interferon-γ, 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 remodelling in a multicentre clinical trial of HF patients[4]. A research has 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.

Recommendations for the use of *n*-3 PUFA supplementation are included in several guidelines for the prevention of CHD[7–9]. Previous epidemiological researches found that supplementation of *n*-3 PUFA 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 remodelling of HF patients[12], and *n*-3 PUFA reduced the levels of inflammation factors to prevent abnormal LV remodelling. In the GISSI-HF trial, 1 g daily *n*-3 PUFA 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-ischaemic HF patients[15]. The OMEGA-REMODEL trial suggested that dietary supplementation of high-dose *n*-3 PUFA reduced LV remodelling and inflammatory biomarkers[16]. However, other clinical trials reported that *n*-3 PUFA supplementation provides less beneficial cardiovascular outcomes on patients[17–19]. 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 *n*-3 PUFA supplementation on LV remodelling 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 (*n*-3 OR *n*-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 *n*-3 PUFA supplementation (both dietary supplements and capsules of *n*-3); (b) participants were patients who were diagnosed as CHF; (c) provided information about cardiac function and (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), ischaemic cardiomyopathy (ICM), ICM/ DCM), BMI, daily dosage of *n*-3 PUFA, duration, total dosages of *n*-3 PUFA, 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 values and standard deviations). Total dosages were calculated as (daily dosage) × (total number of days at the time of examination) (one month was equivalent to 30 d). 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 *n*-3 PUFA intervention SD. For the LV remodelling indices, including LVEF, LVESV, LVEDV, LVESD, LVEDD, TNF-α, IL-6 and Hs-CRP, most of the literature provided the mean values and standard deviations 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, mean values and standard deviations were converted with the information of median, interquartile range and sample size using an estimation method published by Hozo and colleagues[22]. 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[22].

Quality assessment of included studies

The quality of all included randomised controlled trials (ten 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 analysed and scored the prospective studies.

Statistical analyses

The primary study outcomes were assessed by the changes of LV remodelling indices including LVEF, LVESV, LVEDV, LVESD and LVEDD, and circulating inflammatory mediators including TNF-α, IL-6 and Hs-CRP in both n-3 PUFA 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). For the continuous variables, the pooled effects were presented as weighted mean difference (WMD) with 95 % CI. I^2 test was used to evaluate the clinical heterogeneity, and $I^2 \geq 50$ % indicated obvious heterogeneity[23]. 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 n-3 PUFA and LV remodelling 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 eighty 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 fifty-seven studies, and twelve studies were eligible for the current analysis based on the selection criteria, of which ten studies were randomised controlled trials[4,14,16,24–30], and two studies were prospective studies[31,32]. The flow diagram of the initial literature search and trial selection is shown in Fig. 1.

Baseline characteristics

Baseline characteristics of included trials are summarised in Table 1. A total of 2162 participants were included, with age (years) range from 55·1 to 74·0. The twelve 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[24]) countries. Baseline and follow-up LVEF scores were available in eleven studies. In the eleven clinical trials, nine studies were diagnosed as HFrEF (LVEF ≤ 40 %)[4,14,24,26–31], whereas two studies were diagnosed as HFpEF (LVEF ≥ 50 %)[16,32]. Changes in LVESV[14,25,28–30] and LVEDD[14,24,27,29,30] were available in five trials. LVEDV[14,25,29,32] and LVESD[23,27,29,30] data were evaluated in four studies. TNF-α[4,27–29,31], IL-6[4,27–29] and Hs-CRP[4,27,31,32] were evaluated from data extracted from 5, 4, 4 studies, respectively. Eleven trials (1804 participants) assessed cardiac function using echocardiography, while 1 study (358 participants)[16] used cardiac MRI (cMRI). The aetiology of CHF participants was classified as ICM in four studies[16,26,30,32], DCM in three studies[4,28,29] and both ICM and DCM in four studies[14,24,27,31], respectively.

Administration details of n-3 PUFA and placebo groups

In all included studies, the daily dosage of n-3 PUFA varied from 1 to 5·2 g/d, with duration ranged from 3 to 12 months. The daily dosage of EPA ranged between 360 and 1860 mg and DHA ranged from 240 to 1500 mg, compared with a recommended dietary intake of 250–2000 mg/d for each[33]. Eleven trials evaluated the combined effect of n-3 PUFA supplementation[4,14,16,24–30,32] while one trial assessed independent effect of EPA[31]. The placebo composition included olive oil[25,28,29], linoleic acid[16] or no pills[23]. The supplements of placebo groups were not mentioned in the remaining seven studies[4,14,26,27,30–32].

Study quality assessment

The quality assessment of randomised controlled trials was analysed by Cochrane Collaboration's Tool and generally of good quality (online Supplementary Fig. S1). In the Revised JADAD's Scale, four studies scored 4[25–28], four studies scored 5[14,24,29,30] and the other two studies scored 7[4,16] (online Supplementary Table S1a). The two prospective studies were assessed by the Newcastle–Ottawa Scale, and the result showed one study scored 7[31] while the other scored 6[32] (online Supplementary Table S1b).

Effects of n-3 PUFA supplementation on ventricular remodelling

Compared with placebo groups, n-3 PUFA supplementation improved LVEF by a WMD of 2·52 (95 % CI 1·25, 3·80, $I^2 = 87·8$ %, Fig. 2(a)). Additionally, n-3 PUFA supplementation significantly decreased LVESV (WMD = –3·22, 95 % CI –3·67, –2·77, $I^2 = 0·0$ %, Fig. 2(b)). The pooled results indicated that the differences were not statistically significant for LVEDV (Fig. 2(c)), LVESD (Fig. 2(d)) or LVEDD (Fig. 2(e)). The I^2 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 categorised by LVEF, including HFpEF (LVEF ≥ 50 %), HF with borderline EF (LVEF 41 % to 49 %) and HFrEF (LVEF ≤ 40 %)[2]. In the current study, LVEF improved by 2·02 % in HFrEF patients taking n-3 PUFA (WMD = 2·02, 95 % CI 0·70, 3·34, $I^2 = 87·0$ %), while it increased by 4·59 % in HFpEF group (WMD = 4·59, 95 % CI 0·87, 8·31, $I^2 = 78·1$ %). In the aetiology subgroup, the LVEF was prominently increased in DCM patients (WMD = 4·49, 95 % CI 2·72, 6·26, $I^2 = 0·0$ %), while no significant improvement could be observed in the ICM and ICM/DCM subgroups. Subgrouping according to BMI showed no significant improvement in LVEF in either normal weight patients (BMI = 18·5–24·9 kg/m^2) or pre-obesity patients (BMI = 25·0–29·9 kg/m^2). Based on the regions, results from studies in the western countries revealed a significant association between improvement in LVEF and n-3 PUFA intake (WMD = 2·19, 95 % CI 0·92, 3·47, $I^2 = 86·8$ %).
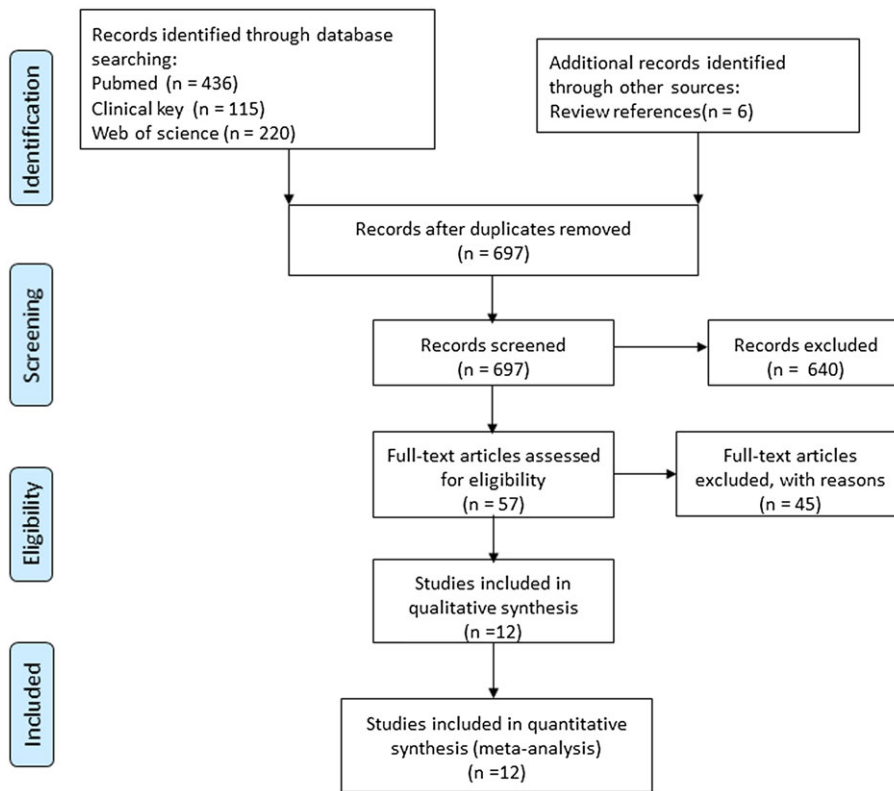
Fig. 1. Flow diagram of the systematic review and meta-analysis.

Dosage accumulation effect of n-3 PUFA on left ventricular ejection fraction improvement

Further subgroup analysis was performed to examine whether the efficacy on LVEF was associated with the dosage of *n*-3 PUFA supplementation (Table 2). Average daily dosage, duration and total dosages for all included studies are summarised in Table 1. Subgrouping according to average daily intake showed *n*-3 PUFA at a dosage of 1–3 g/d (WMD = 3·60, 95 % CI 0·86, 6·33, $I^2 = 87\cdot5$ %) and ≥ 3 g/d (WMD = 2·96, 95 % CI 1·25, 3·80, $I^2 = 0\cdot0$ %) had beneficial effects in LVEF, whereas ≤ 1 g/d showed no significant improvement. Duration seemed to have effects on LVEF improvement, as a trend favoured a longer *n*-3 PUFA 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, 3·80, $I^2 = 95\cdot2$ %) intervention subgroup. Of note, subgroup analysis according to total *n*-3 PUFA intake showed a dosage-dependent accumulation effect on LVEF improvement: there was no significant improvement in LVEF at a dosage of ≤ 300 g and a high dosage 300–600 g, while a much higher dosage (≥ 600 g) achieved a greater benefit in LVEF scores (WMD = 5·23, 95 % CI 2·31, 8·15, $I^2 = 77\cdot1$ %).

Effects of n-3 PUFA intake on circulating inflammatory mediators

Increased secretion of circulating inflammatory mediators was associated with the pathogenesis and progression for cardiac mortality and ventricular remodelling[34,35]. Results showed that both TNF-α (WMD = −3·48, 95 % CI −4·67, −2·30, $I^2 = 97\cdot9$ %, Fig. 3(a)) and IL-6 (WMD = −3·85, 95 % CI −6·05, −1·64, $I^2 = 94\cdot2$ %, Fig. 3(b)) levels significantly decreased in *n*-3 PUFA treated group compared with placebo groups. Hs-CRP was also decreased in *n*-3 PUFA treated group (WMD = −0·23, 95 % CI −0·41, −0·05, $I^2 = 80\cdot8$ %, Fig. 3(c)).

Publication bias and sensitivity analysis

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

Discussion

This meta-analysis of twelve studies had several findings: first, *n*-3 PUFA treatment contributed to improve the LVEF and LVESV. Second, the benefits of *n*-3 PUFA 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 600 g. Third, *n*-3 PUFA supplementation reduced the levels of circulating TNF-α, IL-6 and Hs-CRP. Collectively, these results supported that *n*-3 PUFA supplementation had a positive association with cardiac function and support its current recommendation in CHF patients[36].

LV remodelling is generally accepted as a critical factor in the progression of CHF. During the process of ventricular

Table 1. Baseline characteristics of included trials are summarised
(Mean values and standard deviations; numbers and percentages)

Authors (year)	Country	Group	Age (years) Mean	SD	Male number (%)		Daily dosage (g/d)	Duration (months)	Total dosages (g)	Patients	BMI (kg/m²) Mean	SD
Skou HA et al. (2001)	Denmark	n-3 PUFA	64	5	N/A		5·2	3	468	ICM	N/A	
		placebo	61	8								
Radaelli A et al. (2006)	Italy	n-3 PUFA	59·4	2·5	14	93	2	4	240	ICM	N/A	
		placebo	60·1	2·7	10	100						
Zhao YT et al. (2009)	China	n-3 PUFA	74	6	27	71	2	3	180	ICM/	24·7	3·6
		placebo	71	10	28	76				DCM	24·0	2·9
Nodari S et al. (2009)	Italy	n-3 PUFA	61·09	11·22	21	95·4	5 g/d 1 month	6	300	DCM	N/A	
		placebo	64·82	9·46	19	86·4	1 g/d 5 months					
Ghio S et al. (2010)	Italy	n-3 PUFA	65	10	274	87·8	1	12	360	ICM/	N/A	
		placebo	65	11	238	80·4				DCM		
Nodari S et al. (2011)	Italy	n-3 PUFA	61	11	64	95·5	5 g/d 1 month	12	810	DCM	25·9	2·3
		placebo	64	9	56	84·9	2 g/d 11 months				25·7	2·22
Moertl D et al. (2011)	Austria	n-3 PUFA	58·6	7·0	12	86	1	3	90	DCM	27·0	3·3
		n-3 PUFA	61·9	9·6	13	100	4		360		27·8	5·0
		placebo	55·1	12·7	12	75	N/A		N/A		28·0	5·6
Kojuri J et al. (2013)	Iran	n-3 PUFA	56	N/A	22	58	2	6	360	ICM	N/A	
		placebo	58	N/A	20	61						
Kohashi K et al. (2014)	Japan	n-3 PUFA	71·4	7·7	60	84·5	1·8	12	648	ICM/	23·7	2·0
		placebo	66·2	11·9	59	86·8				DCM	23·1	2·9
Heydari B et al. (2016)	USA	n-3 PUFA	60	10	148	82	4	6	720	ICM	29	5·4
		placebo	58	10	140	79					29	5·6
Chrysohoou C et al. (2016)	Greece	n-3 PUFA	63	12·8	80	79·2	1	6	180	ICM/	28·72	3·88
		placebo	63·4	14·6	83	87·4				DCM	27·6	4·76
Campos-Staffico AM et al. (2019)	Brazil	n-3 PUFA	58	11	165	76	≥ 1·7	6	≥ 306	ICM	26·8	5·0
		n-3 PUFA	60	10	152	74	< 1·7		< 306		25·9	5·1

DCM, dilated cardiomyopathy; ICM, ischaemic cardiomyopathy; N/A, not applicable.

remodelling, 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 remodelling assessment due to its clear contrast resolution and high reproducibility[39]. However, only one study used cMRI in the current study, which demonstrated that n-3 PUFA significantly inhibited the LVESV index and myocardial fibrosis[16]. Further large-scale studies using cMRI are needed to evaluate the effect of n-3 PUFA on cardiac remodelling.

n-3 PUFA have attracted interest as a possible addition to available lifestyle measures and medications for the prevention of CVD[40]. Previous study showed the cardioprotective mechanisms of n-3 PUFA against HF, including anti-inflammatory; intervention of cardiac energy metabolism; modification of cardiac ion channels; improvement of vascular endothelial and modulation of autonomic nervous system activity[41–43]. The American Heart Association advisory board recommended n-3 PUFA supplementation (1 g/d, 2 years) in CHF patients for the secondary prevention of CVD death[36]. Meanwhile, several animal studies provide solid evidence that n-3 PUFA supplementation not only prevents diastolic and systolic dysfunction but also improves abnormal ventricular remodelling[44,45]. A previous meta-analysis performed in 2012 indicated n-3 PUFA 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 n-3 PUFA in

CHF patients and suggested that n-3 PUFA supplementation could lead to improvement in LVEF and reduction in LVESV.

Additionally, our results showed the recovery of LVEF by n-3 PUFA supplementation in both HFpEF and HFrEF patients. Though HFpEF subgroup is relatively small (two trials), the LVEF improvement was evident. As a disease with limited evidence-based treatment options, our data support the application of n-3 PUFA supplementation in HFpEF patients. For HFrEF patients suffering from a progressive LVEF decay, n-3 PUFA supplementation could help to preserve LVEF level with slight but significant improvements. Furthermore, recent research showed that n-3 PUFA may determine long-term change in weight and the high dosage of n-3 PUFA 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 n-3 PUFA 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 n-3 PUFA, might contribute to a severe deficiency of n-3 PUFA[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 favourable trend on LVEF in eastern subgroup.

n-3 PUFA 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
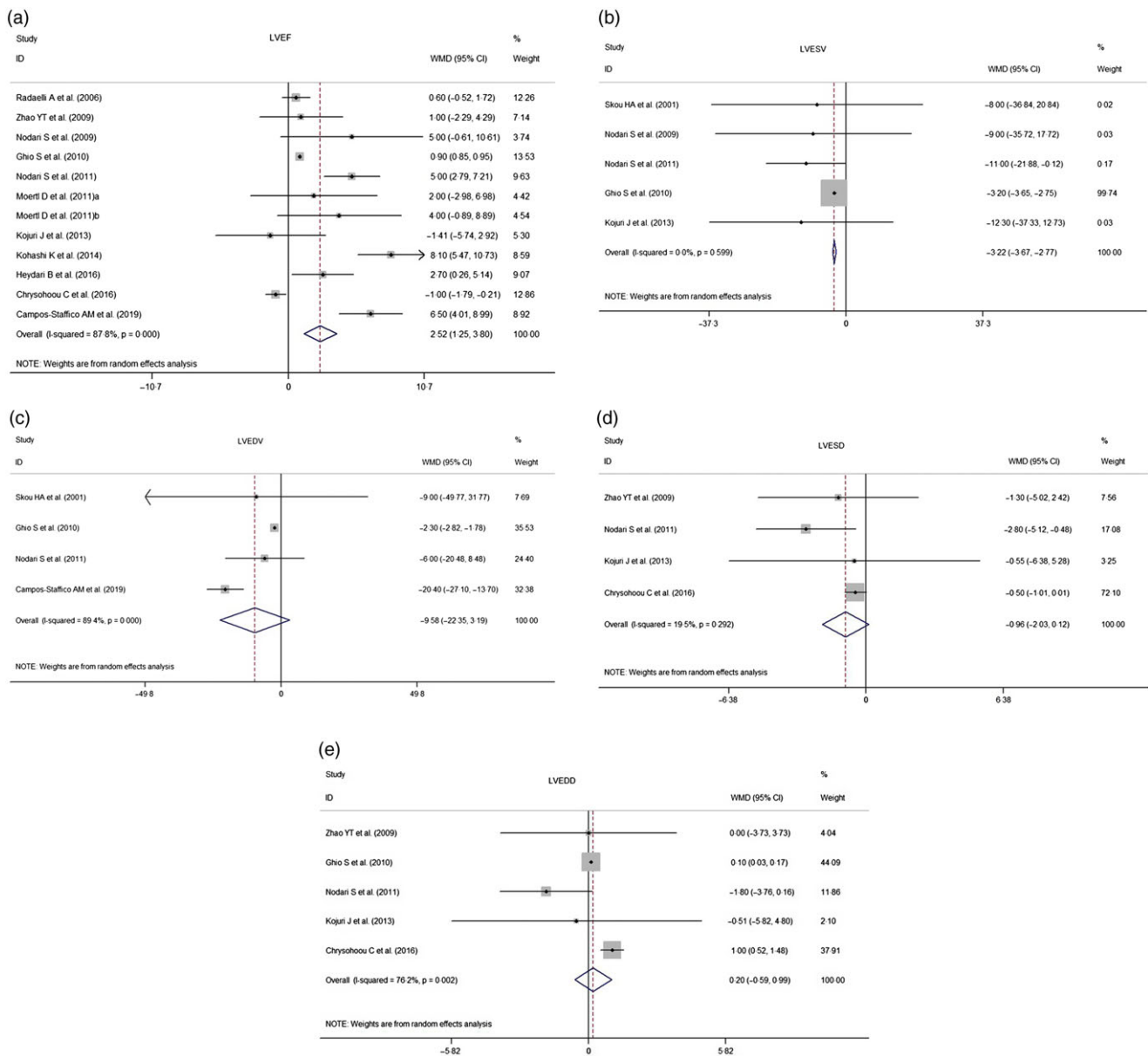
Fig. 2. Forest plot indicated the effects of *n*-3 PUFA supplementation on cardiac function. (a) Effect of *n*-3 PUFA supplementation on LVEF. (b)–(e) Effect of *n*-3 PUFA supplementation on LVESV, LVEDV, LVESD and LVEDD. I^2 indicated the degree of studies heterogeneity; WMD, weighed mean difference; LVEF, left ventricular ejection fraction; LVESV/LVESD, left ventricular end systolic volume/diameter; LVEDV/LVEDD, left ventricular end diastolic volume/diameter.

of *n*-3 PUFA (EPA + DHA or EPA-only) at a dose of 4 g/d is an effective and safe option for reducing TAG as monotherapy or as an adjunct to other lipid-lowering agents[50,51]. However, clinical trials reported inconsistent benefits from *n*-3 PUFA on cardiovascular events, even in trials using the same high dose of *n*-3 PUFA (4 g/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 remodelling during infarct convalescence remains the strongest favourable risk predictor and serves as a common mechanistic pathway that reduces mortality, sudden cardiac death and heart failure incidence[56]. However, the cardiac remodelling 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 *n*-3 PUFA correlated with a favourable effect on LVEF. Additionally, it should be noted that the two included studies in the ≥ 3 g/d subgroup had a relative short duration (3–6 months), while five out of seven included studies in the 1–3 g/d subgroup had a longer duration (6–12 months). As both daily dose and duration might be influencing factors for the effects of *n*-3 PUFA, we speculated that the accumulated dosage, indicative for the two factors, might serve as a comprehensive parameter to evaluate the effects of *n*-3 PUFA. Though the included

Table 2. Subgroup analysis of *n*-3 PUFA in CHF patients
(Numbers; 95 % confidence intervals)

Subgroup		Studies _n_: references	Overall effect WMD	95 % CI	Heterogeneity I^2, %
LVEF	≤ 40 %	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.* (2009); Nodari S *et al.* (2011); Moertl D *et al.* (2011); Kojuri J *et al.* (2013); Kohashi K *et al.* (2014)	2·02	0·70,3·34	87·0
	≥ 50 %	2: Heydari B *et al.* (2016); Campos-Staffico AM *et al.* (2019)	4·59	0·87,8·31	78·1
Aetiology	ICM	4: Heydari B *et al.* (2016); Radaelli A *et al.* (2006); Kojuri J *et al.* (2013); Campos-Staffico AM *et al.* (2019)	2·27	−0·76,5·29	85·4
	ICM/DCM	4: Ghio S *et al.* (2010); Chrysohoou C *et al.* (2016); Zhao YT *et al.* (2009); Kohashi K *et al.* (2014)	1·84	−0·20,3·88	94·1
	DCM	3: Nodari S *et al.* (2009); Nodari S *et al.* (2011); Moertl D *et al.* (2011)	4·49	2·72,6·26	0·0
BMI	18·5–24·9	2: Zhao YT *et al.* (2009); Kohashi K *et al.* (2014)	4·62	−2·34,11·58	90·8
	25·0–29·9	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)	3·15	−0·05,6·34	91·3
Location	Western	8: 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)	2·19	0·92,3·47	86·8
	Eastern	3: Zhao YT *et al.* (2009); Kojuri J *et al.* (2013); Kohashi K *et al.* (2014)	2·73	−3·16,8·62	89·2
Dosage of *n*-3 PUFA	≤ 1 g/d	3: Ghio S *et al.* (2010); Chrysohoou C *et al.* (2016); Moertl D *et al.* (2011)	0·19	−1·53,1·90	90·9
	1–3 g/d	7: Radaelli A *et al.* (2006); Zhao YT *et al.* (2009); Nodari S *et al.* (2009); Nodari S *et al.* (2011); Kojuri J *et al.* (2013); Kohashi K *et al.* (2014); Campos-Staffico AM *et al.* (2019)	3·60	0·86,6·33	87·5
	≥ 3 g/d	2: Heydari B *et al.* (2016); Moertl D *et al.* (2011)	2·96	1·25,3·80	0·0
Duration	< 6 months	3: Radaelli A *et al.* (2006); Zhao YT *et al.* (2009); Moertl D *et al.* (2011)	0·84	−0·17,1·85	0·0
	= 6 months	5: Heydari B *et al.* (2016); Chrysohoou C *et al.* (2016); Nodari S *et al.* (2009); Kojuri J *et al.* (2013); Campos-Staffico AM *et al.* (2019)	2·25	−1·26,5·77	90·1
	> 6 months	3: Ghio S *et al.* (2010); Nodari S *et al.* (2011); Kohashi K *et al.* (2014)	4·53	0·02,3·80	95·2

WMD, weighted mean difference; LVEF, left ventricular ejection fraction.

trials were limited, our data suggested that a sufficient accumulated dosage (≥ 600 g) was essential for *n*-3 PUFA mediated LVEF improvements (Table 2).

But, the high heterogeneity was the major challenge to clarify the associations of *n*-3 PUFA 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 remodelling[57]. The induction of cytokines (such as IL-6, TNF-*α*) may be involved in the pathogenesis of adverse remodelling, cardiac dysfunction and ultimately HF. Persistent dysregulated inflammation response might induce cardiac hypertrophy, damage myocardial contractility and finally contribute to LV remodelling[58]. Clinically, patients with higher degrees of inflammation, as measured by circulating N-terminal-pro-type B natriuretic peptide and Hs-CRP, had increased morbidity and mortality[59]. Daily intake of *n*-3 PUFA could attenuate inflammatory response, which further prevent the progression of HF or ST-elevation MI patients[27,32,60]. In HF patients, *n*-3 PUFA can reduce the circulating level of the pro-inflammatory cytokines activated by nuclear transcription factor kappa B, such as TNF-*α*, IL-1 and IL-6[61]. In a rat model of MI, increasing expression of IL-6, TNF-*α* and IL-1 in myocardium was significantly associated with increased LVEDD[62]. Our results suggested that *n*-3 PUFA supplementation significantly reduced the expression of inflammation cytokines including TNF-*α*, IL-6 and Hs-CRP. These effects might explain how *n*-3 PUFA supplementation attenuated the cardiac remodelling.

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 *n*-3 PUFA on patients with HF with borderline EF yet, so the present meta-analysis could not give any evidence on *n*-3 PUFA supplementation in this population. Third, other measurements and circulating inflammatory mediators such as left atrial volumes and NT-pro-B natriuretic peptide might possibly link to ventricular remodelling and need further investigation.

Conclusion

This meta-analysis demonstrated that *n*-3 PUFA supplementation was associated with a substantial improvement of LV function and remodelling in patients subjected to CHF. *n*-3 PUFA intake also decreased the levels of circulating pro-inflammatory factors in CHF patients. The accumulated dosage of *n*-3 PUFA consumption is vital for its cardiac protective role.
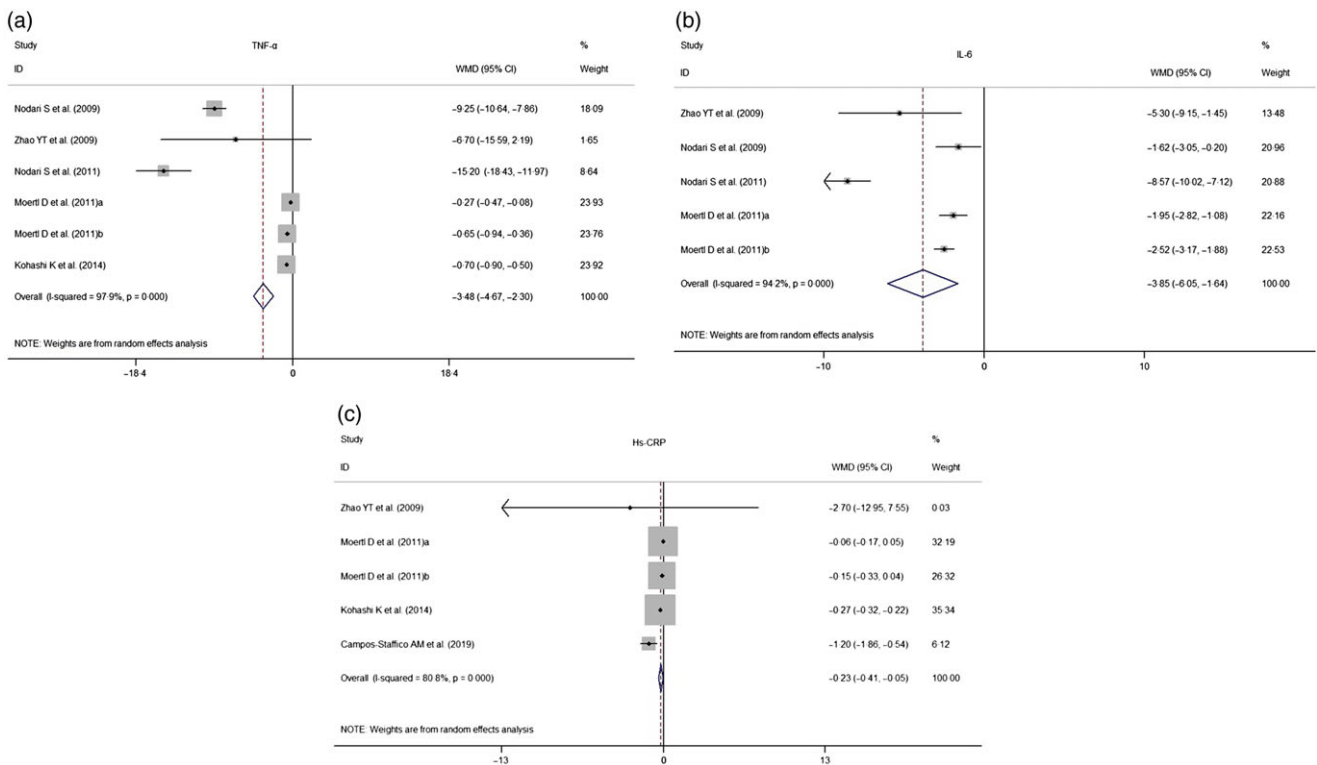
Fig. 3. Forest plot of the effect of *n*-3 PUFA on inflammatory cytokines. (a) The effect of *n*-3 PUFA on TNF-*α*. (b) The effect of *n*-3 PUFA on IL-6. (c) The effect of *n*-3 PUFA on Hs-CRP. Hs-CRP, hypersensitive c-reactive protein.
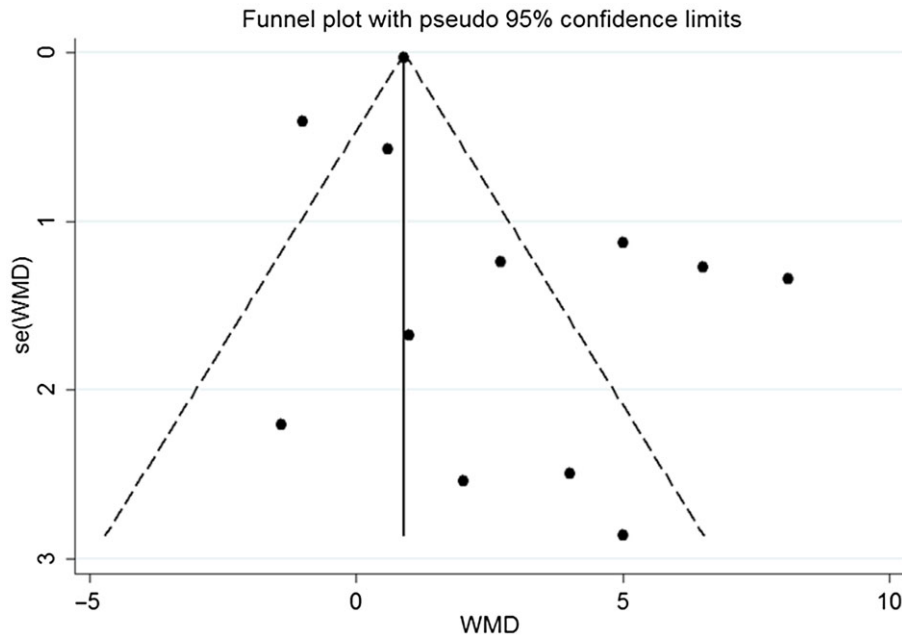

Fig. 4. Funnel plot of the effect of *n*-3 PUFA on LVEF. LVEF, left ventricular ejection fraction.

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Supplementary material

For supplementary material accompanying this paper visit https://doi.org/10.1017/S0007114521004979

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