Omega-3 polyunsaturated fatty acid supplementation and non-alcoholic fatty liver disease
A meta-analysis of randomized controlled trials

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Abstract
Background: Clinical trials examining the therapeutic benefit of omega-3 polyunsaturated fatty acids (ω-3 PUFAs) on nonalcoholic fatty liver disease (NAFLD) have reported inconsistent results. We performed a meta-analysis of randomized controlled trials (RCTs) examining the effect of ω-3 PUFA supplementation on NAFLD, and provide substantial evidence on whether ω-3 PUFA supplementation has a favorable effect for treating NAFLD.

Methods: We searched the PubMed, Cochrane Library, Springer Link, China National Knowledge Infrastructure (CNKI), Wanfang, and Chinese Scientific and Technological Journal (VIP) databases for RCTs on oral ω-3 PUFA supplementation in patients with NAFLD. The data were pooled; meta-analyses were conducted using random-effect or fixed-effect models.

Results: Eighteen studies involving 1424 patients were included. We found a significant benefit for ω-3 PUFAs vs control for liver fat, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, triglycerides, insulin resistance, and glucose. However, there was significant interstudy heterogeneity. Subgroup and regression analyses showed no significantly clear methodologic discrepancy. Publication bias and serious adverse events were not detected.

Conclusions: Our meta-analysis suggests that ω-3 PUFA supplementation may decrease liver fat and hepatic enzyme parameters. However, more large-scale, well-designed RCTs are needed to confirm the effect of ω-3 PUFA supplementation on these parameters.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CNKI = China National Knowledge Infrastructure, CVD = cardiovascular disease, DBP = diastolic blood pressure, GGT = γ-glutamyl transferase, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment of IR, IR = insulin resistance, ITT = intention-to-treat, LDL-C = low-density lipoprotein cholesterol, MS = metabolic syndrome, NAFLD = nonalcoholic fatty liver disease, NASH = nonalcoholic steatohepatitis, PPAR-α = peroxisome-proliferator-activated receptor α, PUFA = polyunsaturated fatty acid, RCT = randomized controlled trial, RR = relative risk, SBP = systolic blood pressure, SREBP-1c = sterol-regulatory-element-binding protein 1c, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TGs = triglycerides, VIP = Chinese Scientific and Technological Journal, WC = waist circumference, WMD = weighted mean difference.

Keywords: meta-analysis, nonalcoholic fatty liver disease, omega-3 polyunsaturated fatty acids
1. Introduction
Nonalcoholic fatty liver disease (NAFLD) encompasses a histological spectrum that ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), which can lead to cirrhosis and liver cancer and is projected to be the principal factor for liver transplantation by 2020.[1,2] The prevalence of NAFLD is steadily increasing and is currently 20% to 30% in Western countries and 5% to 18% in Asia.[3-5] NAFLD is more prevalent in patients with metabolic diseases such as obesity and type 2 diabetes mellitus (T2DM),[6] and is recognized as the hepatic manifestation of the metabolic syndrome (MS).[7,8] Moreover, its prevalence is expected to increase in the near future as an aftermath of the increasing adoption of a sedentary lifestyle and unhealthy diet.[9,10] Therefore, new therapeutic approaches for managing NAFLD are warranted.

Currently, the primary treatment for NAFLD is lifestyle therapy, which achieves weight loss and reducing insulin resistance (IR) and hepatic steatosis/inflammation in patients with NAFLD.[7,8] However, the effectiveness of lifestyle modification is low and wanes with time, underlining the need for pharmacologic therapy.[11] Small cohorts have trialed pharmacotherapies including vitamin E,[9] pioglitazone,[10] and obeticholic acid[11]; their effectiveness is limited by poor compliance. Therefore, there is a pressing need to develop more effective and safe agents for this common disease.

Studies investigating the dietary patterns of patients with NAFLD vs controls have reported that individuals with NAFLD have lower omega-3 polyunsaturated fatty acid (ω-3 PUFA) intake and higher ω-6/ω-3 PUFA intake ratio[12-14]; animal studies have confirmed these findings.[15,16] ω-3 PUFAs may reduce hepatic lipogenesis and inflammation, representing a simple and practical alternative therapy. Therefore, dietary guidelines on nutrient intake for improving NAFLD generally recommend increasing the intake of ω-3 PUFAs in NAFLD patients with diet alteration and exercise, which are imperative for achieving weight loss and reducing insulin resistance (IR) and hepatic steatosis/inflammation in patients with NAFLD.[7,8] However, the effectiveness of lifestyle modification is low and wanes with time, underlining the need for pharmacologic therapy.[17] Small cohorts have trialed pharmacotherapies including vitamin E,[9] pioglitazone,[10] and obeticholic acid[11]; their effectiveness is limited by poor compliance. Therefore, there is a pressing need to develop more effective and safe agents for this common disease.

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2. Methods
2.1. Data sources and search strategy
We searched English and non-English language publications on the PubMed, Cochrane Library, Springer Link, China National Knowledge Infrastructure (CNKI), Wanfang, and Chinese Scientific and Technological Journal (VIP) databases from inception to May 2018. The search terms used were: omega-3, ω-3, ω-3, PUFA, fish oil, EPA, DHA, PUFAs, docosapentaenoic acid, docosahexaenoic acid, NAFLD, NASH, NAFLD, nonalcoholic steatohepatitis, fatty liver, and hepatic steatosis. The reference lists of reviewed articles were manually searched for additional relevant studies.

2.2. Study selection
We determined the inclusion and exclusion criteria a priori. Studies were excluded if they met the following inclusion criteria: population of any age or sex or ethnic origin with NAFLD diagnosed based on histologic or imaging evidence; intervention involving oral administra-
removed. Full texts were obtained for articles where the title and abstract alone were insufficient for determining the eligibility for inclusion. An eventual 18 studies involving 1424 patients were deemed eligible for inclusion in the study: 13 were published in English and 5 were published in languages other than English. Table 1 summarizes the characteristics of the included studies. All included studies were RCTs published in 2008 to 2016: 55.83%, 25.56%, and 18.61% had been conducted in Asian, Caucasian, and European populations, respectively. Fifteen studies involved adult participants; 3 studies involved child participants. All studies used ω-3 PUFA supplementation only. Seven studies advised lifestyle modification for overweight or obese participants. The median ω-3 PUFA supplementation dose was 2.7g/d (range, 0.25–5.00g/d) and the median treatment duration was 6 months (range, 3–18 months). Only slight abdominal discomfort was reported in the reviewed studies, and there were no reports of serious adverse effects.

3.2. Methodologic quality

Table 2 and Figure 2 present the results of the study quality assessment. Most included studies had low risk of bias in sequence generation, allocation concealment, blinding, and analysis, and were of high methodologic quality.

3.3. Effect of ω-3 PUFA supplementation on liver fat

Seven studies reported data on liver fat improvement. There was significant heterogeneity among these studies ($I^2 = 60.7\%, \ P = .018$). Therefore, a random-effect model was used. The meta-analysis showed that participants treated with ω-3 PUFAs were more likely to have improvement in liver fat compared with placebo-treated participants (RR = 1.56, 95% CI: 1.23–1.97) (Fig. 3).

3.4. Effect of ω-3 PUFAs on hepatic enzyme parameters

Fourteen, 12, and 8 studies had sufficient data for inclusion in analyses of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transferase (GGT), respectively. There was significant heterogeneity among these studies (ALT: $I^2 = 86.4\%, \ P < .001$; AST: $I^2 = 91.2\%, \ P < .001$). The random-effect model showed that ω-3 PUFA therapy had a statistically significant beneficial effect on ALT and AST; the pooled SMDs and their 95% CIs were −0.50 (95% CI: −0.88 to −0.11) and −0.54 (95% CI: −1.04 to −0.05), respectively. There was no significant heterogeneity among these studies for GGT ($I^2 = 41.6\%, \ P = .101$). The fixed-effect model showed significant pooled SMD for the efficacy of ω-3 PUFA therapy on GGT (SMD = −0.48, 95% CI: −0.64 to −0.31) (Figs. 4–6).
3.5. Effect of ω-3 PUFAs on serum lipids

Sixteen, 15, 11, and 9 studies had sufficient data for inclusion in analyses of triglycerides (TGs), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), respectively.

There was significant heterogeneity for TG ($I^2 = 79.6\%, P < .001$), TC ($I^2 = 90.3\%, P < .001$), and HDL-C ($I^2 = 74.8\%, P < .001$). The random-effect model showed significant pooled SMD favoring ω-3 PUFA therapy vs control for TG (SMD = –0.47, 95% CI: –0.76 to –0.19). However, there were no significant pooled SMDs for the efficacy of ω-3 PUFA therapy on TC (SMD = –0.09, 95% CI: –0.30 to 0.33) and HDL-C (SMD = 0.24, 95% CI: –0.08 to 0.55). There was no significant heterogeneity among these studies for LDL-C ($I^2 = 21.9\%, P = .249$). The fixed-effect model showed no significant pooled SMD for the efficacy of ω-3 PUFA therapy on LDL-C (SMD = –0.10, 95% CI: –0.25 to 0.06) (Figure S1, http://links.lww.com/MD/C460).

3.6. Effect of ω-3 PUFAs on glucose metabolism

Eight, 8, and 7 studies had sufficient data for inclusion in analyses of homeostasis model assessment of IR (HOMA-IR), glucose, and insulin, respectively.

We found no significant heterogeneity among these studies (HOMA-IR: $I^2 = 16.6\%, P = .299$; glucose: $I^2 = 43.0\%, P = .092$; insulin: $I^2 = 20.7\%, P = .272$). The fixed-effect model showed a significant pooled MD favoring ω-3 PUFA therapy vs...
control for HOMA-IR (WMD = −0.40, 95% CI: −0.58 to −0.22) and glucose (SMD = −0.25, 95% CI: −0.43 to −0.06). However, there was no significant pooled SMD for the efficacy of ω-3 PUFA therapy on insulin (SMD = −0.08, 95% CI: −0.29 to 0.13) (Figure S2, http://links.lww.com/MD/C460).

### 3.7. Effect of ω-3 PUFAs on anthropometric parameters

Nine, 5, 2, and 3 studies had sufficient data for inclusion in analyses of body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP), respectively.
We found no significant heterogeneity among the studies for BMI ($I^2 = 42.5\%, \ P = .084$), WC ($I^2 = 5.1\%, \ P = .378$), SBP ($I^2 = 0.0\%, \ P = 1.000$), and DBP ($I^2 = 0.0\%, \ P = .958$). The fixed-effect models showed no significant pooled WMD for the efficacy of ω-3 PUFA therapy on BMI (WMD $= -0.30$, 95% CI: $-0.71$ to $0.11$), WC (WMD $= 2.24$, 95% CI: $-0.17$ to $4.65$), SBP (WMD $= 1.00$, 95% CI: $-4.40$ to $6.40$), and DBP (WMD $= -0.14$, 95% CI: $-2.49$ to $2.21$) (Figure S3, http://links.lww.com/MD/C460).

3.8. Publication bias and sensitivity analysis
Both Begg and Egger tests did not reveal statistically significant publication bias for any of the main outcomes (Table S1, http://links.lww.com/MD/C460). This was confirmed based on visual inspection of the corresponding funnel plot (Figure S4, http://links.lww.com/MD/C460). In the influence analyses, 2 study appeared to influence the pooled data.\cite{28,36} So we excluded the study by Liu\cite{36} from the analyses of ALT, AST, and GGT and excluded the study by Boyraz et al\cite{28} from the analysis of SBP. The final results of sensitivity analysis were shown in Figure S5, http://links.lww.com/MD/C460.

3.9. Subgroup and meta-regression analysis
Hypothesizing that differences in the effects of ω-3 PUFA supplementation on liver fat, ALT, AST, and GGT were not at random, we explored prespecified potential sources of heterogeneity. These included exposure characteristics, that is, dose per day (<3g/d or ≥3g/d) and treatment duration (≤6 months or >6 months), and participant characteristics, that is, ethnicity (European, Asian, or Caucasian) and age (adult or child). Consequently, more than half of the subgroup’s heterogeneity was decreased inordinately (Figure S6–S9, http://links.lww.com/MD/C460).

A meta-regression analysis was performed to investigate the effect of exposure and participant characteristics in determining the heterogeneity of estimates. The results indicated that the attributions of these covariates ranged from 1.32% to 52.19%; however, no statistical significant associations were observed between them (Table S1, http://links.lww.com/MD/C460).

3.10. Adverse events
Overall, ω-3 PUFA supplementation was well-tolerated, and there were only minor gastrointestinal symptoms. However, the short duration of the trials, which did not exceed 2 years, prevents any conclusion from being drawn on the long-term safety of the proposed treatments.

4. Discussion
The present investigation is an updated systematic review of RCTs exploring the efficacy of ω-3 PUFA supplementation for...
treated NAFLD. Despite the significant heterogeneity in study design, there was high methodologic quality and absence of evidence of publication bias. The 8 RCTs included in the study suggest that ω-3 PUFA supplementation is associated with a beneficial effect on liver fat in humans. In addition, we found that ω-3 PUFA therapy had a significant beneficial effect on ALT, AST, GGT, TG, IR, and glucose. However, ω-3 PUFA supplementation was not significantly associated with TC, HDL-C, LDL-C, insulin, SBP, DBP, BMI, and WC. These results suggest that ω-3 PUFAs have therapeutic potential against NAFLD.

The effects of ω-3 PUFA supplementation on NAFLD have remained largely unchanged since a similar review by Parker et al in 2012. The authors, who first reported ω-3 PUFA supplementation in humans with NAFLD, found that ω-3 PUFA therapy had a beneficial effect on liver fat, whether they included only RCTs or all trials. A recent meta-analysis by Lu et al demonstrated that ω-3 PUFA supplementation improves liver fat. Our meta-analysis also confirms this conclusion. ω-3 PUFAs may influence NAFLD through specific mechanisms. They are known to downregulate sterol-regulatory-element-binding protein 1c (SREBP-1c) and upregulate peroxisome proliferator-activated receptor α (PPAR-α), which would favor fatty acid oxidation and reduce steatosis. Moreover, ω-3 PUFAs can give rise to resolvins, which are anti-inflammatory. However, ω-3 PUFAs cannot be synthesized de novo, but oral administration can alter their levels. Based on these observations, it has been suggested that ω-3 PUFA supplementation is efficacious for managing NAFLD.

Elevated liver enzymes in patients with NAFLD are associated with a clinically significant risk of developing end-stage liver disease. It is unclear whether ω-3 PUFA supplementation affects the levels of hepatic enzymes such as ALT, AST, and GGT. Parker et al reported that ω-3 PUFA therapy had a significant beneficial effect on AST and a tendency toward a beneficial effect on ALT, but that these effects were not significant after analyzing data from only RCTs. However, a meta-analysis of another 7 RCTs involving 442 patients reported a significant effect of ω-3 PUFAs on ALT and a nonsignificant effect on AST and GGT, while a recent meta-analysis showed a significant effect of ω-3 PUFAs on GGT and a nonsignificant effect on ALT and AST. In the present study, ω-3 PUFA therapy had significant effects on ALT, AST, and GGT. The possible reasons for the inconsistent findings are that the previous meta-analyses excluded trials involving children (<18 years old); by contrast, we did not restrict participant age in our study. The 5 studies excluded from our analysis for being non-RCTs have been included in other meta-analyses, while we included the 7 most recent RCTs published in the past 3 years. The previous reviews involved 9, 7, and 10 trials, respectively, which were all published in English; however, we included in our study eighteen RCTs published in both English and languages other than English; 2 previous studies assessed the risk of bias using the Jadad score; here, we used the Cochrane risk of bias tool.

Figure 5. Forest plot of analysis of effect of omega-3 polyunsaturated fatty acids on aspartate aminotransferase.
The NAFLD is recognized as the hepatic manifestation of MS, which is associated with increased risk for T2DM and cardiovascular disease (CVD). Therefore, the potential hepatic benefits of ω-3 PUFA therapy should be considered in combination with its effects on MS and cardiometabolic risk factors. Based on the cohorts included in the present meta-analyses, in which pooled MDs were measured, ω-3 PUFA supplementation benefited TG, IR, and glucose statistically significantly; however, the changes for TC, HDL-C, LDL-C, insulin, SBP, DBP, BMI, and WC were nonsignificant. Earlier systematic reviews have reported improvements in TG following ω-3 PUFA therapy, and the improvements in IR and glucose are novel findings. Although the mechanism of ω-3 PUFAs for preventing MS and CVD adverse outcomes is unclear, the effect of ω-3 PUFAs may be due to their ability to decrease TG levels, BP, and glucose. There is also clear evidence from meta-analysis that ω-3 PUFAs are linked to glucose, IR, and insulin secretion capacity. However, our data suggest that the reductions in SBP and DBP are not significant.

There were several limitations in our study, especially heterogeneity. Although we detected statistical significant heterogeneity among some of the RCTs, exploration of the potential source of heterogeneity revealed that it may have been due to differences in treatment dose, treatment duration, ethnicity and age. However, the meta-regression analysis indicated no significant associations between them, and the random-effect model was applied. There may also have been other sources of heterogeneity, such as clinician skill, different measurement techniques, and inconsistent definition of disease criteria. In addition, the amount of ω-3 PUFAs would be easily obtained through diet, and the dietary intakes were not uniform across the studies. These heterogeneities may have restricted the interpretation of the pooled effects.

The strengths of this meta-analysis include: the large sample size enabled assessment of the association of ω-3 PUFAs and NAFLD and rendered it more powerful. Second, most included studies had low risk of bias in key domains, and were of high methodologic quality. Third, the prospective nature of the included studies avoided the influence of recall bias. Fourth, the compliance rates were high in most of the studies, which were determined by tablet-counting. These data provide a comprehensive view of the association between ω-3 PUFAs and NAFLD based on the current evidence.

In conclusion, the present analysis provides an updated systematic review and meta-analysis involving only RCTs on ω-3 PUFAs and NAFLD. The results suggest that ω-3 PUFA supplementation can improve liver fat, ALT, AST, GGT, TG, IR, and glucose in patients with NAFLD. So ω-3 PUFA supplementation may improve metabolic and cardiovascular risk factors and surrogate makers for liver disease progression. However, further studies are warranted to confirm whether ω-3 PUFA supplementation improves hard outcomes including mortality, progression to cirrhosis, or histologic inflammations. In addition, it is too early to validate these findings on liver fat, ALT, AST, GGT, and TG, given the heterogeneity among the studies. More large-scale, well-designed RCTs are needed to confirm the effect of ω-3 PUFA supplementation on these parameters. And future studies also need to confirm the dose-dependent effects and

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Figure 6. Forest plot of analysis of effect of omega-3 polyunsaturated fatty acids on γ-glutamyl transferase.
quantify the long-term durability and safety of ω-3 PUFA supplementation.

**Author contributions**

Xian-E Peng, Jian-Hui Yan and Bing-Jie Guan conceived the study and wrote the manuscript. Jian-Hui Yan and Hai-Yan Gao contributed to collect data and evaluate literature. Jian-Hui Yan and Bing-Jie Guan analyzed and interpreted the data. All authors reviewed the manuscript.

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