INPLASY PROTOCOL

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Support: **Yes**

Review Stage at time of this submission: **Piloting of the study selection process.**

Conflicts of interest:
None.

Efficacy and safety of omega-3 fatty acids on liver-related outcomes in patients with nonalcoholic fatty liver disease: a protocol for a systematic review and meta-analysis

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Review question / Objective: **Does omega-3 fatty acids supplementation have beneficial effects on liver histology in patients with NAFLD? Does omega-3 fatty acids supplementation have beneficial effects on aminotransferase levels in patients with NAFLD? Are the effects of omega-3 fatty on the liver-related outcomes impacted by such factors as: Duration of supplementation? Doses of supplementation? Age (children versus adults)?**
Condition being studied: **NAFLD is emerging as a major health problem worldwide due to its high prevalence and the associated risk of liver-related consequences (liver cirrhosis and HCC) . The role of n-3 PUFA as a potential treatment for NAFLD has attracted much attention. Numerous studies have demonstrated the improvement effect of PUFA therapy on liver fat in NAFLD patients but yielded controversial effects on other liver-related outcomes, such as liver enzymes and liver histology.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 May 2020 and was last updated on 03 May 2020 (registration number INPLASY202050008).

INTRODUCTION

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METHODS

Participant or population: Patients with a diagnosis of NAFLD/NASH.

Intervention: Omega-3 fatty acids with any doses, primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Comparator: Placebo or any other active treatment.

Study designs to be included: Only Randomized Controlled Trials (RCTs) will be included.

Eligibility criteria: The following were the inclusion criteria: a) study design: RCTs with any follow-up duration and sample size were allowed; b) population: patients of any age or sex or ethnic origin with a definitive diagnosis of NAFLD or NASH by histologic or imaging evidence (ultrasound, computed tomography or magnetic resonance imaging (MRI); c) intervention: n-3 PUFA at any dose and route; d) control: placebo, or other active agents; e) outcomes: liver-related outcomes, such as liver histology (steatosis score, hepatocellular ballooning score, lobular inflammation score, fibrosis score and NAFLD activity score (NAS)), liver enzymes (alanine aminotransferase (ALT), aspartate transaminase (AST) and γ-glutamyl transferase (GGT)), and adverse events.

Information sources: Two authorswill independently search databases including Medline, the Cochrane Library, EMBASE, and Web of science until July 2020. According to the PICOS principle, the keywords of our search terms were: ((“eicosapentaenoic acid” OR “docosahexaenoic acid” OR “omega-3” OR “ω-3” OR “EPA” OR “DHA” OR “PUFA” OR “n-3 PUFA”) AND (“non-alcoholic fatty liver disease” OR “non alcoholic fatty liver disease” OR “NAFLD” OR “nonalcoholic fatty liver disease” OR “nonalcoholic fatty liver*” OR “nonalcoholic steatohepatiti*” OR “non-alcoholic steatohepatitis*” OR “fatty liver*” OR “NASH”). The ClinicalTrials.gov registry will also be searched for unpublished trials and the authors will be contacted for any additional information if necessary. Relevant references from included studies will be sought to retrieve additional eligible studies.

Main outcome(s): Liver histology (steatosis score, hepatocellular ballooning score, lobular inflammation score, fibrosis score and NAFLD activity score (NAS))

Additional outcome(s): Liver enzymes (alanine aminotransferase (ALT), aspartate transaminase (AST) and γ-glutamyl transferase (GGT)), and adverse events.

Quality assessment / Risk of bias analysis: Based on the Cochrane Handbook for Systematic Reviews (version 5.3.0), we will assess the methodological quality of all studies. The risks of bias will be classified as low, unclear, or high by evaluating the 7 components as random sequence generation, allocation concealment, blinding of outcome assessment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and other bias. Two independent reviewers will conduct this assessment, and a third reviewer will be consulted for any disagreements.

Strategy of data synthesis: We will calculate the weighted mean difference (WMD) and 95% confidence intervals (CIs) of all outcomes: liver histology (steatosis score, hepatocellular ballooning score, lobular inflammation score, fibrosis score and NAS, liver enzymes: ALT, AST and GGT, and adverse events. If raw data are not reported, we will impute unreported means ± SDs using established methods via other information (e.g., CIs or median and

interquartile range, etc) provided in the publication. If only providing data pre and post-intervention period, we will calculate the change of mean ± SDs using the formula recommended in the Cochrane Handbook Version 5.1.0.

Subgroup analysis: Subgroup analyses will be prespecified according to study population (children and adults), doses of supplementation (≤3 g/day and > 3 g/day), duration (≤6 months and > 6 months), and type of supplementation (DHA alone, EPA alone and the combination of EPA and DHA).

Sensibility analysis: Sensitivity analyses will be performed by removing a single trial each time and repeating the meta-analyses to assess the reliability and stability of the pooled results.

Language: English.

Country(ies) involved: China.

Keywords: Non-alcoholic fatty liver disease, omega-3 polyunsaturated fatty acids, liver histology, liver enzymes, protocol, systematic review.

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