HHS Public Access

Author manuscript

Curr Opin Clin Nutr Metab Care. Author manuscript; available in PMC 2020 March 01.

Published in final edited form as:

Curr Opin Clin Nutr Metab Care. 2019 March ; 22(2): 103–110. doi:10.1097/MCO.0000000000000539.

Omega-3 Fatty Acids and Nonalcoholic Fatty Liver Disease in Adults and Children: *Where Do We Stand?*

Melinda H. Spooner and **Donald B. Jump***

Nutrition Program, School of Biological and Population Health Sciences, Linus Pauling Institute, Oregon State University, Corvallis, OR, USA

Abstract

Purpose of review: Nonalcoholic fatty liver disease (**NAFLD**) is the most common chronic fatty liver disease worldwide. The incidence of NAFLD parallels the prevalence of obesity. Moreover, NAFLD can progress to nonalcoholic steatohepatitis (**NASH**), cirrhosis and primary hepatocellular cancer (**HCC**). As such, NAFLD has become a major public health concern. We discuss recent clinical trials and meta-analyses evaluating the efficacy of $C_{20–22}$ ω3 polyunsaturated fatty acids (**PUFA**) to attenuate pre-existing NAFLD in adults and children.

Recent findings: Humans with NAFLD and NASH; and preclinical mouse models of NASH, have a high abundance of hepatic saturated (**SFA**) and monounsaturated (**MUFA**) fat, but a low abundance of hepatic $C_{20–22}$ ω3 PUFA. This change in hepatic fat type and abundance is associated with hepatic lipotoxicity, inflammation, oxidative stress and fibrosis. Recent meta-analyses and clinical trials evaluated the capacity of $C_{20–22}$ ω3 PUFA dietary supplementation to improve health outcomes in adults and children with pre-existing NAFLD. Diets supplemented with docosahexaenoic acid (**DHA**, 22:6,ω3) alone or with eicosapentaenoic acid (**EPA**, 20:5,ω3) are safe and effective at lowering liver fat in NAFLD patients. However, outcomes are mixed with respect to $C_{20–22}$ ω3 PUFA attenuation of more severe NAFLD markers, such as hepatic injury, inflammation and fibrosis.

Summary: These studies suggest that dietary supplementation with $C_{20–22}$ ω3 PUFA should be considered as a viable and effective option to lower liver fat in obese adults and children with NAFLD.

Keywords

ω3 PUFA; NAFLD; NASH; liver fat; inflammation; fibrosis

Introduction

The accumulation of neutral lipids to >5% of total liver weight, not linked to alcohol consumption or other liver diseases, is the hallmark of **NAFLD** (1*, 2, 3). NAFLD is strongly associated with obesity (3, 4); and it is the most common chronic fatty liver disease

***Address correspondence to:** Donald B. Jump, Ph.D., School of Biological and Population Health Sciences, 107A Milam Hall, Oregon State University, Corvallis, OR 97331-5109, Phone: 541-737-4007; FAX: 541-737-6914, Donald.Jump@oregonstate.edu.

Conflicts of Interest: The authors declare no conflicts of interest.

in developed nations (5, 6*). Both adults and children can present with NAFLD; and gender, ethnicity and genetic polymorphisms contribute to the onset and progression of NAFLD (7, 8). Obesity, dyslipidemia, metabolic syndrome (**MetS**) and type 2 diabetes mellitus (**T2DM**) are the four dominant risk factors for NAFLD (8). NAFLD ranges in severity from benign steatosis to nonalcoholic steatohepatitis (**NASH**); and NASH can progress to cirrhosis, primary hepatocellular carcinoma (**HCC**) and liver failure (6*, 8, 9). Approximately 30% of the US population has some form of chronic fatty liver disease (6). As such, NAFLD has emerged as a major public health concern (6*, 7).

The worldwide public health burden of NAFLD is significant, affecting 10–24% of the total population (4). In the United States, 24–45% of the population is estimated to have some level of NAFLD (5). This increases to 60–95% in the obese population (4, 10*). NASH develops in 10–30% of those with benign steatosis, and 20–30% of these patients progress to develop cirrhosis (5, 6*, 7, 8, 10*, 11). By 2020, NASH leading to cirrhosis is predicted to be the primary cause of liver transplantation in the United States (6*, 8).

Five to 10% of children between the ages of 2 to 18 years old present with NAFLD; and NAFLD ranges from 36% to 80% in obese children (3, 9, 12, 13*, 14). Autopsy studies of ethnically diverse children reported that liver histology-identified NAFLD ranged from 4.5% −13% in similar populations from New York City and San Diego (15*). Childhood NAFLD increases the risk for developing cardiovascular disease (**CVD**), MetS, cirrhosis, and advanced liver disease in early adulthood (14, 16*). Furthermore, a 20-year landmark study on the natural history of NAFLD in children reported that NAFLD progressed to NASH with fibrosis (17**). These young NAFLD patients had a 13.8-fold increased risk of requiring a liver transplant or risk of death than healthy age- and sex-matched children (17**).

NAFLD Treatment Strategies

Clearly, there is a need for safe and effective therapies to prevent and treat NAFLD and NASH. There remains, however, no FDA-approved therapies for NAFLD (8). Instead, the primary clinical approach for NAFLD therapy is lifestyle modifications to promote weight loss. Current macronutrient modifications aim to improve MetS, T2DM, and reduce inflammation; and includes decreasing consumption of simple sugars, trans-fats, and SFA, reducing the ratio of ω6 PUFA to ω3 PUFA and increasing low-glycemic foods and MUFA (4, 8, 11). A 3 – 10% loss of body weight is associated with decreased hepatosteatosis and liver injury (plasma ALT, AST) (11, 18, 19).

Patient non-compliance, however, remains a major concern when using lifestyle interventions to improve health outcomes (3, 6*, 8, 20, 21). Accordingly, pharmacological agents aimed at treating specific NAFLD targets are currently under development (8, 20, 22). For example, elafibranor, a dual peroxisome proliferator-activated receptor (**PPARα & β**) and pioglitazone, a PPARγ agonist, act to increase fatty acid oxidation and insulin sensitivity, respectively; while other approaches target oxidative stress, immunological and fibrotic pathways (20, 22, 23). Yet, adverse drug effects arising from off-target mechanisms often occur (7, 21). Consequently, the American Association for the Study of Liver Diseases (**AASLD**) and the European Association for the Study of Liver (**EASL**) approve only

pioglitazone and vitamin E for treating NASH in adults (18, 23). While the AASLD only approves vitamin E for the pediatric NAFLD patient (9, 18).

The rationale for using ω3 PUFA in NAFLD therapy

NAFLD develops because of abnormal fat metabolism leading to the hepatic accumulation of neutral lipids, i.e., diacylglycerols, triacylglycerols (**TAG**) and cholesterol esters (8). The key mechanisms regulating hepatic fat content include *de novo* lipogenesis, fatty acid oxidation, fat uptake from the circulation and its assimilation into lipids and VLDL assembly and secretion (8). $C_{20–22}$ ω3 PUFA regulate all of these pathways, at least in part, by controlling the activity and/or abundance of transcription factors regulating the expression of genes encoding proteins involved in these pathways [see reviews (7, 8)].

While diets like the western diet contain essential fatty acids (**EFA:** linoleic acid, **LA**, 18:2, ω6 and α-linolenic acid, **ALA**, 18:3, ω3), EFAs in these diets represent a minor fraction of total dietary fat consumed (8). Moreover, LA is more abundant than ALA in the western diet (7, 8). While ≤4% of ingested ALA is converted to $C_{20–22}$ ω3 PUFA in humans (8), this level of conversion may be affected by gender, ethnic or genetic polymorphisms within genes encoding enzymes involved in $C_{20–22}$ PUFA, particularly the desaturases (Fads1, Fads2) (24–28). A meta-analysis of genome-wide association studies (**GWAS**) from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium found that genetic variations in *Fads1* and *Fads2* were associated with high levels of ALA versus EPA and DPA (29).

In addition, $C_{20–22}$ PUFA synthesis is subject to feedback inhibition by excess dietary $C_{20–22}$ PUFA due to the decreased expression of a key transcription factor controlling PUFA synthesis, i.e., SREBP1c (30–33). This mechanism likely accounts for the $C_{20–22}$ ω3 PUFA-mediated suppression of blood & tissue arachidonic acid levels (20:4,ω6). Excess dietary DHA is retro-converted to eicosapentaenoic acid (EPA, 20:5,ω3) and docosapentaenoic acid (ω3 DPA, 22:5,ω3) through peroxisomal retro-conversion (34). DHA retro-conversion to 20:5,ω3 predominates over Elovl2- and Fads2-mediated conversion of EPA to tetracosahexaenoic acid (24:6,ω3) (35). While this retro-conversion pathway is also inefficient, i.e., <2% of DHA is converted to EPA in humans, this pathway provides a mechanism to increase blood and tissue levels EPA, DPA and DHA from dietary DHA (36).

Since NAFLD & NASH in humans and preclinical mouse models is associated with a decline in blood and tissue PUFA content (6*, 10*, 37), a logical approach is to increase hepatic $C_{20–22}$ ω3 PUFA through dietary supplementation. A recent preclinical study demonstrated that addition of DHA to the western diet fed to obese mice with pre-existing NASH decreased hepatic fat, inflammation and expression of genes involved in fibrosis (6). This preclinical study provided a proof-of-concept that DHA supplementation at 2% total calories attenuates NASH progression.

Recent meta-analyses and clinical trials assessing ω3 PUFA in NAFLD therapy.

We recently reviewed clinical trials and meta-analyses published between 2006 and 2016 that examined the capacity of ω3 PUFA to treat NAFLD (8). We now examine clinical trials and meta-analyses published since 2016 (Tables 1 & 2) (10*, 13*, 16*, 37, 38**, 39**, 40, 41*, 42). There is considerable overlap of the clinical trials assessed in the meta-analyses described in Table 1. The number of subjects ranged from 263 to 1132, and included children and adults with diagnosed NAFLD. The interventions used DHA alone, a combination of EPA + DHA or ω3 PUFA preparations from fish or seal oil. Doses of ω3 PUFA and duration of treatment ranged from 0.25 to 6.8 grams of oil/day for 3–25 months, respectively. The criteria for inclusion in the clinical study was evidence of NAFLD.

The consensus of the meta-analyses is that hepatic steatosis improves in adults and children with biopsy, MRI, or ultrasound proven NAFLD following $C_{20–22}$ ω3 PUFA treatment (10*, 13*, 16*, 37, 38**, 39**, 40, 41*, 42). Plasma lipids were largely improved; triglycerides and markers of hepatic injury, i.e., ALT, were significantly reduced in several of the studies reported in the meta-analyses (10*, 13*, 16*, 37, 38**, 39**, 40, 41*, 42).

Musa-Veloso et al (41*) reported NAFLD biomarkers concurred with previous meta-analyses and RCTs. Hepatic biopsy data from adult NASH patients, however, revealed no significant improvement in histological criterion by which NASH features were assessed (i.e., fibrosis, hepatocellular ballooning, steatosis, and lobular inflammation). Further, no meta-analysis reported on ω3 PUFA effects on plasma and/or hepatic inflammation or fibrosis markers. However, recent studies in both humans (8) and rodents (6*, 8) indicate that EPA and DHA do not have equivalent effects on systemic inflammation, hepatic lipid content or hepatic fibrosis (8). DHA is more effective than EPA at reducing plasma markers of systemic inflammation and hepatic fibrosis markers.

Tissue and blood $C_{20–22}$ ω3 PUFA enrichment are important features to include in human clinical trials. A meta-analysis performed on 10 case control studies revealed hepatic and blood DHA content was significantly lower ($p < 0.001$), while SFA, MUFA, and ARA were significantly higher ($p < 0.044 – p < 0.001$) in NAFLD cases (13*). Whereas 11 RCTs treating NAFLD patients with a variety of ω3 PUFA resulted in a trend toward improved steatosis ($p = 0.051$) and significant improvement NAFLD plasma markers ($p \leq 0.002$) (13*).

Six clinical trials, not subject to secondary meta-analysis have appeared since 2017 (Table 2). All used forms of ω3 PUFA that included the $C_{20–22}$ ω3 PUFA, i.e., EPA & DHA. The dose ranged from 0.945 to 4 g/day for 3–18 months. Children (<18 years of age) were included in 2 of the 6 studies. All studies included patients with pre-existing NAFLD, and the number of patients varied from 7–60 per study. All studies included ω3 PUFA effects on plasma markers of ω3 PUFA status except Zöhrer et al (40). Some included markers of liver injury; one study included an assessment of hepatic histology, inflammation and fibrosis (40).

Most studies reported that increasing dietary $C_{20–22}$ PUFA increased plasma and/or RBC levels of $C_{20–22}$ ω3 PUFA indicating treatment compliance (1, 10*, 37, 38**, 39**). Both liver fat and plasma ALT were significantly reduced, representing suppression of hepatosteatosis and reduced liver injury (1, 10*, 37). One report indicated that AST, another marker of tissue injury, was not significantly affected by ω3 PUFA treatment (37). While ALT is expressed in both hepatic and non-hepatic tissues, AST has broad expression in multiple tissues (https://www.proteinatlas.org/). The differential effect of ω3 PUFA on plasma ALT and AST likely reflects tissue-specific differences in the response to $C_{20–22}$ ω3 PUFA.

One study (38**) used a proteomic approach to assess ω3 PUFA effects on hepatic pathways. They reported that supplementation with ω3 PUFA improved pathways involved in lipid metabolism, ER stress, cellular respiration and extracellular matrix. A pilot study by Hodson, et al (39**) reported that a 2% increase in RBC ω3 PUFA content was inversely associated with a decline in VLDL-TG, fasting DNL (measured in VLDL-TG) and β-hydroxybutyrate, but positively associated with increased hepatic sensitivity to insulin. Furthermore, Tobin et al (10*) reported in a post-hoc analysis that NAFLD patients, treated for 24 weeks with EPA + DHA ethyl esters and baseline fatty liver index (**FLI**) ≥40, may benefit more from EPA + DHA treatment than those with <40 FLI.

While there is a paucity of childhood NASH/NAFLD studies, one pediatric NASH study reported significant improvement in severe hepatic steatosis and several histological features of NASH ($p<0.01$) (40). The study involved 6 months of treatment with DHA (250 mg/d), choline (391 IU) & vitamin E (201 mg) per day, followed by an additional 6 months on a hypocaloric diet with increased physical activity (40). This study, however, had several interventional components that prohibits a conclusive statement of DHA efficacy in this pediatric NASH population. Spahis et al (37) reported that adolescents appear to exhibit broad spectrum NAFLD improvement, including significant changes in fasting insulin, and homeostasis model assessment of insulin resistance (**$HOMA^{IR}$**) in addition to plasma lipids, FLI, and hepatic injury markers, with a dose of 1.2 g/d for as little as 6 months of treatment. One meta-analysis focused exclusively on ω3 PUFA efficacy in children (<18 years of age) (16*). Hepatic steatosis, as determined by ultrasound, was significantly improved ($p = 0.0001$) across 3 RCTs with an intervention of 250–1300 mg/d of DHA or a mixture of ω3 PUFA for 6 – 12 months (16*). This small meta-analysis had low heterogeneity between the RCTs which, given its sample size was a strength (16*).

Together, these clinical trials provide evidence in support of using high quality $C_{20–22}$ ω3 PUFA to control metabolic parameters linked to NAFLD. The limitations of these clinical trials include small sample size, inconsistent usage of ω3 PUFA type, variations in dose and treatment duration, compliance of the placebo group, an assessment of hepatic inflammation and fibrosis markers and an assessment of genetic polymorphisms within the test population (10*).

CONCLUSION

Strengths and Limitations of using $C_{20–22}$ ω3 PUFA to treat NAFLD

The clinical evidence presented above indicates that $C_{20–22}$ ω3 PUFA are safe and efficacious in the reduction of liver fat in NAFLD patients. A significant advantage of $C_{20–22}$ ω3 PUFA supplementation is that $C_{20–22}$ ω3 PUFA attenuates NAFLD progression without requiring weight loss. Attenuation of disease progression is a significant clinical goal. Furthermore, $C_{20–22}$ ω3 PUFA supplementation effectively lowers plasma triglycerides, a cardio-metabolic disease risk factor. Cardiovascular disease is the primary cause of mortality in NAFLD patients (18).

There are, however, limitations to $C_{20–22}$ ω3 PUFA usage in NAFLD therapy. The clinical evidence indicates that the capacity of $C_{20–22}$ ω3 PUFA to lower blood levels of markers of liver injury (ALT/AST) and inflammation is mixed. Moreover, fibrosis scores are rarely included in clinical studies (Tables 1, 2) (8). The gold standard for fibrosis assessment involves histological evaluation of biopsied liver, a procedure with inherent risk. A preclinical study established that DHA administration to mice with pre-existing NASH lowered hepatosteatosis and suppressed the expression of hepatic inflammation and fibrosis gene expression markers (6*). This treatment, however, did not eliminate fibrosis from the liver. Removal of fibrosis/scarring form the liver requires protease activity to exceed the activity of enzymes generating extracellular matrix, e.g., collagen 1A1 (Col1A1). DHA suppresses expression of enzymes involved in forming and degrading extracellular matrix enzymes. Despite this limitation, DHA blocks NASH progression as well as worsening fibrosis (6*).

Previous reports have described the differential efficacy of DHA versus EPA in the treatment of NAFLD (8). In addition to the poor conversion of EPA to DHA *in vivo* described above, EPA and DHA differentially affect regulatory pathways relevant to the control of NAFLD and its progression to NASH (8). As such, we support the use of high quality DHA or equivalent amounts of EPA + DHA to elevate blood and tissue levels of EPA & DHA in order to attenuate NAFLD progression.

Finally, both epidemiological and genetic studies have indicated a strong link between specific genetic polymorphisms and the incidence of NAFLD. A recent review listed nearly 20 polymorphisms associated with NAFLD; and most polymorphisms were associated with increased disease severity (43). One example is the patatin-like phospholipase domain-containing 3 (PNPLA3) gene. The protein product of this gene is an acyltransferase involved in converting lysophosphatidic acid to phosphatidic acid. The frequency of a specific polymorphism (rs738409; 148M variant) in PNPLA3 in ethnic populations i.e., Hispanics (49%), Caucasians (23%) and African Americans (17%), parallels the prevalence of NAFLD in these populations (44). PNPLA3 expression is regulated by two transcription factors, i.e., sterol regulatory element binding protein 1c (SREBP1c) and carbohydrate regulatory element binding protein (ChREBP) (43, 45). The expression & function of both transcription factors is suppressed by $C_{20–22}$ ω3 PUFA (33). A recent review indicates that patients carrying the rs738409 G-allele 148M variant are more sensitive to ω3 PUFA and statin therapy than patients without this allele (46).

While we have discussed only one NAFLD-linked gene polymorphism, there are many others that encode proteins involved in lipid & glucose metabolism, insulin signaling, stellate cell activation and cell senescence (43, 45–47). As such, including an assessment of gene polymorphisms in future clinical trials focused on NAFLD and ω3 PUFA may provide data to improve clinical care through personalized treatment strategies.

Acknowledgements.

Financial Support and Sponsorship.

This work was supported by the National Institutes of Health grant DK112360.

References and recommended reading

Papers of particular interest, published with the annual review period of review have been highlighted as:

* of special interest

** of outstanding interest

References:

1*. Eriksson JW, Lundkvist P, Jansson PA, Johansson L, Kvarnstrom M, Moris L, et al. Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. Diabetologia. 2018;61(9):1923–34. [PubMed: 29971527] The concentration of DHA in OM3-CA is less than half that of EPA which may contribute to the conclusion of some studies that ω3 PUFA are ineffective in reducing NAFLD features.

2. Kang S, Huang J, Lee BK, Jung YS, Im E, Koh JM, et al. Omega-3 polyunsaturated fatty acids protect human hepatoma cells from developing steatosis through FFA4 (GPR120). Biochim Biophys Acta Mol Cell Biol Lipids. 2018;1863(2):105–16. [PubMed: 29126901]

3. Panera N, Barbaro B, Della Corte C, Mosca A, Nobili V, Alisi A. A review of the pathogenic and therapeutic role of nutrition in pediatric nonalcoholic fatty liver disease. Nutrition Research. 2018;58:1–16. [PubMed: 30340810]

4. Vranesic Bender D, Nutrizio M, Josic M, Ljubas Kelecic D, Karas I, Premuzic M, et al. Nutritional Status and Nutrition Quality in Patients with Non-Alcoholic Fatty Liver Disease. Acta Clin Croat. 2017;56(4):625–34. [PubMed: 29590715]

5. Allen AM, Van Houten HK, Sangaralingham LR, Talwalkar JA, McCoy RG. Healthcare Cost and Utilization in Nonalcoholic Fatty Liver Disease: Real-World Data From a Large U.S. Claims Database. Hepatology. 2018.

6*. Lytle KA, Wong CP, Jump DB. Docosahexaenoic acid blocks progression of western diet-induced nonalcoholic steatohepatitis in obese Ldlr−/− mice. PLoS One. 2017;12(4):e0173376. [PubMed: 28422962] DHA effectively attenuates NASH progression in a preclinical mouse model of western diet induced obesity.

7. Scorletti E, Byrne CD. Omega-3 fatty acids and non-alcoholic fatty liver disease: Evidence of efficacy and mechanism of action. Mol Aspects Med. 2018;64:135–146. [PubMed: 29544992]

8. Jump DB, Lytle KA, Depner CM, Tripathy S. Omega-3 polyunsaturated fatty acids as a treatment strategy for nonalcoholic fatty liver disease. Pharmacol Ther. 2018;181:108–25. [PubMed: 28723414]

9. Mann JP, Valenti L, Scorletti E, Byrne CD, Nobili V. Nonalcoholic Fatty Liver Disease in Children. Semin Liver Dis. 2018;38(1):1–13. [PubMed: 29471561]

10*. Tobin D, Brevik-Andersen M, Qin Y, Innes JK, Calder PC. Evaluation of a High Concentrate Omega-3 for Correcting the Omega-3 Fatty Acid Nutritional Deficiency in Non-Alcoholic Fatty

Liver Disease (CONDIN). Nutrients. 2018;10(8).The authors used fatty liver index (FLI) as a predictor of hepatosteatosis progression risk. Omega 3 PUFA treatment may be more beneficial for patients with high risk of disease progression.

11. George ES, Forsyth A, Itsiopoulos C, Nicoll AJ, Ryan M, Sood S, et al. Practical Dietary Recommendations for the Prevention and Management of Nonalcoholic Fatty Liver Disease in Adults. Adv Nutr. 2018;9(1):30–40. [PubMed: 29438460]
12. Gibson PS, Lang S, Dhawan A, Fitzpatrick E, Blumfield ML, Truby H, et al. Systematic Review: Nutrition and Physical Activity in the Management of Paediatric Nonalcoholic Fatty Liver Disease. J Pediatr Gastroenterol Nutr. 2017;65(2):141–9. [PubMed: 28737568]
13*. Guo XF, Yang B, Tang J, Li D. Fatty acid and non-alcoholic fatty liver disease: Meta-analyses of case-control and randomized controlled trials. Clin Nutr. 2018;37(1):113–22. [PubMed: 28161092] This meta-analysis illustrates the imbalance of blood and hepatic lipids in NAFLD patients versus controls.
14. Mann JP, Tang GY, Nobili V, Armstrong MJ. Evaluations of Lifestyle, Dietary, and Pharmacologic Treatments for Pediatric Nonalcoholic Fatty Liver Disease: A Systematic Review. Clin Gastroenterol Hepatol. 2018.
15*. Fernandes DM, Pantangi V, Azam M, Salomao M, Iuga AC, Lefkowitch JH, et al. Pediatric Nonalcoholic Fatty Liver Disease in New York City: An Autopsy Study. J Pediatr. 2018;200:174–80. [PubMed: 29903531] This study provides vital information on the prevalence of pediatric NAFLD, not previously identified to have liver disease, in diverse populations from two distinct regions of the US.
16*. Chen LH, Wang YF, Xu QH, Chen SS. Omega-3 fatty acids as a treatment for non-alcoholic fatty liver disease in children: A systematic review and meta-analysis of randomized controlled trials. Clin Nutr. 2018;37(2):516–21. [PubMed: 28040302] This small meta-analysis focused on childhood NAFLD. The study concluded that it is important to treat the pediatric population with long-chain ω3 fatty acids
17**. Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S, Benson JT, Enders FB, Angulo P. The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. Gut. 2009;58(11):1538–44. [PubMed: 19625277] This study demonstrates the progressive nature of NAFLD to NASH in children in a long-term study, with links to transplant and survival outcomes. This critical information establishes the importance of identifying at-risk or pre-existing NAFLD children before the disease progresses and becomes detrimental to long term outcomes.
18. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328–57. [PubMed: 28714183]
19. Oh S, Han G, Kim B, Shoda J. Regular Exercise as a Secondary Practical Treatment for Nonalcoholic Fatty Liver Disease. Exercise Medicine. 2018;2.
20. Banini BA, Sanyal AJ. Current and future pharmacologic treatment of nonalcoholic steatohepatitis. Current Opinion in Gastroenterology. 2017;33(3):134–41. [PubMed: 28346237]
21. Sumida Y, Yoneda M. Current and future pharmacological therapies for NAFLD/NASH. J Gastroenterol. 2018;53(3):362–76. [PubMed: 29247356]
22. Albhaisi S, Sanyal A. Recent advances in understanding and managing non-alcoholic fatty liver disease. F1000Res. 2018;7.
23. Eshraghian A Current and emerging pharmacological therapy for non-alcoholic fatty liver disease. World J Gastroenterol. 2017;23(42):7495–504. [PubMed: 29204050]
24. Sergeant S, Hugenschmidt CE, Rudock ME, Ziegler JT, Ivester P, Ainsworth HC, et al. Differences in arachidonic acid levels and fatty acid desaturase (FADS) gene variants in African Americans and European Americans with diabetes or the metabolic syndrome. Br J Nutr. 2012;107(4):547–55. [PubMed: 21733300]
25. Lattka E, Illig T, Koletzko B, Heinrich J. Genetic variants of the FADS1 FADS2 gene cluster as related to essential fatty acid metabolism. Curr Opin Lipidol. 2011;21(1):64–9.
26. Glaser C, Heinrich J, Koletzko B. Role of FADS1 and FADS2 polymorphisms in polyunsaturated fatty acid metabolism. Metabolism. 2010;59(7):993–9. [PubMed: 20045144]

27. Bokor S, Dumont J, Spinneker A, Gonzalez-Gross M, Nova E, Widhalm K, et al. Single nucleotide polymorphisms in the FADS gene cluster are associated with delta-5 and delta-6 desaturase activities estimated by serum fatty acid ratios. J Lipid Res. 2010;51(8):2325–33. [PubMed: 20427696]

28. Mathias RA, Vergara C, Gao L, Rafaels N, Hand T, Campbell M, et al. FADS genetic variants and omega-6 polyunsaturated fatty acid metabolism in a homogeneous island population. J Lipid Res. 2010;51(9):2766–74. [PubMed: 20562440]

29. Lemaitre RN, Tanaka T, Tang W, Manichaikul A, Foy M, Kabagambe EK, et al. Genetic loci associated with plasma phospholipid n-3 fatty acids: a meta-analysis of genome-wide association studies from the CHARGE Consortium. PLoS Genet.7(7):e1002193.

30. Wang Y, Botolin D, Christian B, Busik J, Xu J, Jump DB. Tissue-specific, nutritional, and developmental regulation of rat fatty acid elongases. J Lipid Res. 2005;46(4):706–15. [PubMed: 15654130]

31. Wang Y, Botolin D, Xu J, Christian B, Mitchell E, Jayaprakasam B, et al. Regulation of hepatic fatty acid elongase and desaturase expression in diabetes and obesity. J Lipid Res. 2006;47(9): 2028–41. [PubMed: 16790840]

32. Jump DB, Depner CM, Tripathy S. Omega-3 fatty acid supplementation and cardiovascular disease. J Lipid Res. 2012;53(12):2525–45. [PubMed: 22904344]

33. Jump DB, Tripathy S, Depner CM. Fatty Acid-regulated transcription factors in the liver. Annu Rev Nutr. 2013;33:249–69. [PubMed: 23528177]

34. Sprecher H Metabolism of highly unsaturated n-3 and n-6 fatty acids. Biochimica et Biophysica Acta. 2000;1486:219–31. [PubMed: 10903473]

35. Park HG, Lawrence P, Engel MG, Kothapalli K, and Brenna JT Metabolic fate of docosahexaenoic acid (DHA, 22:6,n-3) in human cells; direct retroconversion of DHA to eicosapentaenoic acid (20:5, n-3) dominates over elongation to tetracosahexaenoic acid(24:6,n-3). FEBS Lett. 2016;590:3188–94. [PubMed: 27543786]

36. Plourde M, Chouinard-Watkins R, Vandal M, Zhang Y, Lawrence P, Brenna JT, et al. Plasma incorporation, apparent retroconversion and beta-oxidation of 13C-docosahexaenoic acid in the elderly. Nutr Metab (Lond). 2011;8:5–9. [PubMed: 21272363]

37. Spahis S, Alvarez F, Ahmed N, Dubois J, Jalbout R, Paganelli M, et al. Non-alcoholic fatty liver disease severity and metabolic complications in obese children: impact of omega-3 fatty acids. J Nutr Biochem. 2018;58:28–36. [PubMed: 29864682]

38**. Okada L, Oliveira CP, Stefano JT, Nogueira MA, Silva I, Cordeiro FB, et al. Omega-3 PUFA modulate lipogenesis, ER stress, and mitochondrial dysfunction markers in NASH - Proteomic and lipidomic insight. Clin Nutr. 2018;37(5):1474–84. [PubMed: 29249532] A short-term, high-dose study using ALA changed key pathways associated with NASH. The authors reported on hepatic lipidomic and proteomic data.

39**. Hodson L, Bhatia L, Scorletti E, Smith DE, Jackson NC, Shojaee-Moradie F, et al. Docosahexaenoic acid enrichment in NAFLD is associated with improvements in hepatic metabolism and hepatic insulin sensitivity: a pilot study. Eur J Clin Nutr. 2017;71(8):973–9. [PubMed: 28294174] This RCT reported that DHA incorporation into RBC was associated with improved hepatic insulin sensitivity and fatty acid metabolism with a high-dose EPA + DHA supplement.

40. Zohrer E, Alisi A, Jahnel J, Mosca A, Della Corte C, Crudele A, et al. Efficacy of docosahexaenoic acid-choline-vitamin E in paediatric NASH: a randomized controlled clinical trial. Appl Physiol Nutr Metab. 2017;42(9):948–54. [PubMed: 28511023]

41*. Musa-Veloso K, Venditti C, Lee HY, Darch M, Floyd S, West S, et al. Systematic review and meta-analysis of controlled intervention studies on the effectiveness of long-chain omega-3 fatty acids in patients with nonalcoholic fatty liver disease. Nutr Rev. 2018;76(8):581–602. [PubMed: 29917092] This study revealed the need for long-term studies to identify the potential for long-chain ω3 PUFA attenuation of NAFLD progression.

42. Yu L, Yuan M, Wang L. The effect of omega-3 unsaturated fatty acids on non-alcoholic fatty liver disease: A systematic review and meta-analysis of RCTs. Pak J Med Sci. 2017;33(4):1022–8. [PubMed: 29067086]

43. Danford CJ, Yao Z, Jiang ZG. Non-alcoholic fatty liver disease: a narrative review of genetics. J Biomed Res. 2018.

44. Setiawan VW, Stram DO, Porcel J, Lu SC, Le Marchand L, Noureddin M. Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: The multiethnic cohort. Hepatology. 2016;64(6):1969–77. [PubMed: 27301913]

45. Chen L, Du S, Lu L, Lin Z, Jin W, Hu D, et al. The additive effects of the TM6SF2 E167K and PNPLA3 I148M polymorphisms on lipid metabolism. Oncotarget. 2017;8(43):74209–16. [PubMed: 29088779]

46. Wang JZ, Cao HX, Chen JN, Pan Q. PNPLA3 rs738409 underlies treatment response in nonalcoholic fatty liver disease. World J Clin Cases. 2018;6(8):167–75. [PubMed: 30148144]

47. Brayner B, Kaur G, Keske MA, Livingstone KM. FADS Polymorphism, Omega-3 Fatty Acids and Diabetes Risk: A Systematic Review. Nutrients. 2018;10(6).

Key Points:

1. NAFLD is a major public health problem in children and adults worldwide.
2. Diet and lifestyle are major contributors to the onset & progression of NAFLD.
3. Diets deficient in ω3 PUFA, like the western diet, are linked to NAFLD.
4. Supplementing diets with $C_{20–22}$ ω3 PUFA, particularly DHA, attenuates hepatosteatosis in children and adults.

Table 1:

Summary of recent meta-analyses investigating efficacy of ω3 PUFA in treating NAFLD/NASH in children and adults.

Study (Year)	# Studies Included	N	Intervention (Dose) [Duration]	Population Age (Years)	Primary Outcomes	Secondary Outcomes
Chen, et al. (2018)(16*)	4 RCTs[1]	263	ω3 PUFA DHA (0.25 – 1.3 g/d) [6 – 12 M]	Children (<18 y)	Hepatic steatosis grade (p<0.0001) 3 ultrasound 1 MRI – not included	
Guo, et al. (2018)(13*)	11 RCTs + 10 CC	536	ω3 PUFA EPA + DHA Not specified (0.8 – 5 g/d) [3 – 18 M]	Adult (≥18 y) Children (<18 y)	ALT (p<0.001) AST (p<0.002) Liver fat (p = 0.051) TAG (p<0.001) Fasting glucose (p = 0.175)	Dose-response (ALT, AST, LF, TAG) / 1 g/day increase of any ω3 PUFA combination (p = 0.021 to p<0.001)
Yu, et al (2017)	13 RCT + Other clinical trials	843	ω3 PUFA ALA + EPA + DHA EPA + DHA DHA Fish oil [3 – 25 M]	Adults (≥18 y) Children (<18 y)	AST (p = 0.19) ALT (p<0.00001) GGT (p = 0.09)	TAG (p<0.003) Fasting glucose (p = 0.95) HDL (p<0.03) LDL (p<0.002)
Musa-Veloso, et al. (2018)(28*)	18 RCTs Parallel or Crossover	1132	ω3 PUFA Fish oil Seal oil EPA EPA + DHA Enriched olive oil Algal oil (0.250 – 6.8 g/d) [1– 24 M]	Adults (≥18 y) Children (<18 y)	AST (p = 0.338) ALT (p=0.046) GGT (p=0.007) Liver fat (MRI or MRS) (p=0.021) Steatosis score (ultrasound) (p<0.001)	NAS (histology) (p=0.105) Fibrosis score (p=0.162) Hepatocellular ballooning score (p=0.443) Lobular inflammation score (p=0.911) Steatosis score (p=0.717)

[1]RCT, randomized controlled trial; PUFA, polyunsaturated fatty acids; DHA, docosahexaenoic acid; MRI, magnetic resonance imaging; CC, case-controlled trials; EPA, eicosapentaenoic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TAG, triacylglyceride, LF, liver fat; GGT, Gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALA, α-linolenic acid; MRS, magnetic resonance spectroscopy; NAS, NAFLD activity score.

Table 2:

Recent clinical trials evaluating the efficacy of ω3 PUFA in treating NAFLD/NASH in children and adults[1].

Author(s) (Year)	Study Design	Population Age, years	N Per Group	Intervention	Placebo	Duration (Months)	Outcomes
Okada, et al. (2017)(25**) Clinical Trial ID: NCT01992809	RCT[1]	Age 18 – 75	Placebo N = 28 ω3 PUFA N = 32	Capsules: ω3 PUFA 945 mg/d ALA (64%) EPA (20%) DHA (16%) Paired Liver & Plasma Biopsy Before & After Treatment	Capsules: Mineral oil 2 ml/d Paired Liver & Plasma Biopsy Before & After Treatment	6	Plasma Lipids: ↑ Plasma ω3 PUFA (p ≤ 0.033) ↓ Plasma Arachidonate (p < 0.05) Liver Proteomics: Improvement in hepatic pathways: Lipid metabolism ER stress Cell Respiration Extracellular Matrix
Tobin et al. (2018)(10*) Clinical Trial ID: NCT02923804	RCT	Age ≥18	Placebo N = 60 MF4637 ω3 PUFA N = 60	Capsules: MF 4637 (BASF AS Lysaker, Norway): EPA 1.38 g + DHA 1.14 g 3X/d Before & After Treatment	Capsules: Olive oil 1 g 3X/d Before & After Treatment	6	RBC Lipids: ↑ RBC ω3 index (p<0.0001) ↑ RBC EPA % (p<0.0001) ↑ RBC DHA % (p<0.0001) ↓ RBC ω6:ω3 ratio (p<0.0001) Liver Fat MRI: Hepatic Fat Fraction (> 40) Placebo: 3.9% ↓ MF4637: 10.1% ↓ (P = 0.009)
Eriksson et al. (2018)(1*) EFFECT-II Study Clinical Trial ID: NCT02279407	RCT	Age: 65.5 ± 5.9 BMI: 31.2 ± 3.5 kg/m2 Liver PDFF 18 ± 9.3 %	Placebo: N = 21 Om3CA N = 20 Dapagliflozin [Forxiga®] N = 21 Both N = 22	Om3CA 4 × 1 g/d Epanova®, (AstraZeneca) Dapagliflozin 1 × 10 mg/d Both Om3CA 4 × 1 g/d Epanova®, Dapagliflozin 1 × 10 mg/d	Placebo Matched capsule & tablets	3	Treatment vs Baseline: Plasma Fatty Acids Om3CA: DHA ↑20–40%; EPA ↑300% Liver Fat (MRI-PDFF) ↓ −15% Om3CA ↓ −13% Dapagliflozin Both: ↓ −21% (p = 0.046) Hepatic Injury Om3CA: No effect Dapagliflozin: ↓ALT, AST, FGF21
Spahis et al. (2018) Clinical Trial ID: NCT02201160	IT	Age 8 – 18 Moderate mNAFLD Steatosis Score (1–2) Severe sNAFLD Steatosis Score (>2, ≤ 5)	Healthy Control N = 20 Moderate NAFLD (mNAFLD) N = 9 Severe NAFLD (sNAFLD)	EPA + DHA 1.2 g + Vit E 15 IU	Healthy Control [Reference Group] mNAFLD sNAFLD	6	sNAFLD only Change: Before Tx versus After Tx BMI, NS ↓ ALT, p =0.0065 AST, NS ↓ HOMA-IR, p = 0.001

Author(s) (Year)	Study Design	Population Age, years	N Per Group	Intervention	Placebo	Duration (Months)	Outcomes
			N = 11				↑ Adiponectin, p = 0.001 ↓ Leptin, p = 0.05 ↑ RBC EPA & DHA ↑ RBC ω3 index ↓ plasma TG, p=0.0001 ↓ Apo B, p = 0.05 ↓ LDL-C. p = 0.05 ↓ FLI, p = 0.04
Hodson et al. (2017)(26**)	RCT Pilot	Age ≥18	Placebo N = 7 Omacor N = 9	Omacor® [Lovaza] EPA + DHA 4 g/d	Olive oil 4 g/d	15 – 18	>2% Increase in RBC DHA Group only ↑ RBC EPA & DHA, p = 0.001 ↓ VLDL-TG, p < 0.05 ↓ Fasting DNL [VLDL-TG], p = 0.01 ↓ β hydroxybutyrate, p < 0.01 ↑ Hepatic insulin sensitivity, p < 0.01
Zöhrer et al. (2017) Clinical Trial ID: NCT01934777	RCT	Age 4 – 16	NASH Placebo N = 20 DHA/ Choline/Vit E N=20	DHA 250 mg/d Choline 201 mg/d Vit E 39 IU/d	Identical Placebo Pearls	6	↓ Steatosis (histologic), p = 0.01 ↓ Ballooning, p = 0.001 ↓ NAS, p = 0.0003 ↓ % Severe steatosis (ultrasound), p = 0.001 ↓ ALT, p = 0.04 ↓ Fasting glucose, p = 0.04

[1]RCT, randomized control trial; IT, intervention trial; IS, Insulin Sensitivity; PP, Postprandial; MRI: magnetic resonance imaging; MF4637, EPA (1.38 g) + DHA (1.14 g) ((BASF AS Lysaker, Norway): PDFF, protein density fat fraction.

OM3-C: EPA + DHA (Epanova®, AstraZeneca) as non-esterified fatty acids; dapagliflozin [Forxiga®, AstraZeneca], sodium glucose lateral transporter #2 (SGLT2) inhibitor; Tx, treatment; BMI, body mass index; PUFA, polyunsaturated fatty acids; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TAG, triacylglyceride, GGT, Gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALA, alpha-linolenic acid; MRS, magnetic resonance spectroscopy; NAS, NAFLD activity score; DNL, de novo lipogenesis; NASH, nonalcoholic steatohepatitis; VLDL-TG, very low-density lipoprotein cholesterol triglyceride; RBC, red blood cell; FLI, fatty liver index; HOMA-IR, homeostasis model assessment of insulin resistance; sNAFLD, severe nonalcoholic fatty liver disease; FGF21, Fibroblast growth factor 21; NS, not significant; ApoB, apolipoprotein B.