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Lifestyle Interventions including Nutrition, Exercise, and Supplements for Nonalcoholic Fatty Liver Disease in Children

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease among children. Lifestyle interventions, such as diet and exercise, are frequently recommended. Children with NAFLD have a distinct physiology that is different from obesity alone and has the potential to influence lifestyle treatments. Studies of diet alone in the treatment of pediatric NAFLD have focused on sugar and carbohydrate, but did not indicate any one dietary approach that was superior to another. For children who are obese and have NAFLD, weight loss may have a beneficial effect regardless of the diet used. Exercise is widely believed to improve NAFLD because a sedentary lifestyle, poor aerobic fitness, and low muscle mass are all risk factors for NAFLD. However, there have been no randomized controlled trials of exercise as a treatment for children with NAFLD. Studies of the combination of diet and exercise suggest a potential for improvement in serum alanine aminotransferase activity and/or magnetic resonance imaging liver fat fraction with intervention. There is also enthusiasm for the use of dietary supplements, however, studies in children have shown inconsistent effects of vitamin E, fish oil, and probiotics. This review presents the available data from studies of lifestyle intervention and dietary supplements published to date, and highlights challenges that must be addressed in order to advance the evidence base for the treatment of pediatric NAFLD.

Keywords

nonalcoholic fatty liver disease; nonalcoholic steatohepatitis; obesity; hypertension; dyslipidemia; insulin resistance; diet; nutrition; exercise; physical activity; dietary supplements; vitamins; probiotics; children; adolescents; pediatrics

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in children with an estimated prevalence of 9.6% in the United States [1]. NAFLD encompasses a broad spectrum of liver disease severity ranging from isolated steatosis to steatohepatitis (NASH) and fibrosis. NAFLD in children can progress rapidly and does reach end stage liver disease in some adolescents. Moreover, having NAFLD in childhood may be an important risk factor for HCC in adulthood [2–4]. There are no approved pharmacological therapies for NAFLD in children.

Therapeutic lifestyle interventions, typically focused on nutrition and exercise, are commonly recommended for the treatment of NAFLD. The joint practice guideline from the American Association for the Study of Liver Disease (AASLD), the American College of Gastroenterology (ACG), and the American Gastroenterology Association (AGA) advocate lifestyle modifications as treatment for NAFLD [5]. However, specific recommendations are not provided regarding type, intensity, or duration of diet or exercise.

Our aim was to review the available literature pertaining to lifestyle interventions in the treatment of NAFLD in children. For the purposes of this review, we considered studies of nutrition, exercise, and/or dietary supplements in children with known or suspected NAFLD.

METHODS

We performed a structured keyword search in PubMed to identify articles from peer-reviewed journals written in English between January 1, 1990 and August 31, 2015 that evaluated the efficacy of lifestyle interventions. Search parameters included: NAFLD, fatty liver, hepatic steatosis, and NASH. These were then restricted by age using the terms pediatric, child, and adolescent. To be included in this review, articles had to be original clinical studies of children with NAFLD or hepatic steatosis with a measured hepatic outcome, such as serum ALT, hepatic fat fraction, or histology. We excluded review articles and cross-sectional studies. Studies of lifestyle interventions were identified using the terms diet, nutrition, exercise, physical activity, and lifestyle. There were 283 articles obtained, of which 17 met criteria for inclusion in this review (Table 1). Clinical trials of dietary supplements were identified using the terms dietary supplement, vitamins, probiotics, and prebiotics. This search strategy yielded 225 articles, of which 11 met criteria for inclusion (Table 2).

NUTRITION

General Recommendations

According to the American Heart Association (AHA), dietary strategies for all children include: “balancing dietary calories with physical activity”, eating vegetables and fruits daily, limiting juice intake, reducing intake of sugar-sweetened beverages and foods, using nonfat or low-fat milk and dairy products, eating more fish, and reducing salt intake [6].

The National Heart, Lung, and Blood Institute (NHLBI) recommended similar guidelines for children to have a healthy diet. They include the following: beverages should be limited to

water or fat-free unflavored milk, dietary fat should comprise 25–30% of daily caloric intake, and diets should include foods high in fiber [7].

Basis for Recommendations in NAFLD

There have not been any clinical trials of diet as a monotherapy for children with biopsy-proven NAFLD. The importance of clinical trials being done in children with biopsy-proven NAFLD cannot be overstated. Many children who are suspected to have NAFLD based upon serum ALT or liver ultrasound may either not have liver disease or have a liver disease other than NAFLD. Of the overweight or obese children referred to a gastroenterology for elevated serum ALT, only 55% had NAFLD. In addition, elevated serum ALT, defined as two times the upper limit of normal, was shown in overweight and obese children to have a sensitivity of 57% and specificity of 71% for NAFLD [8]. Moreover, liver ultrasound evidence of steatosis has been shown to have a positive predictive value of only 47–62% for NAFLD [9]. The advanced MRI technique of proton density fat fraction has been shown to strongly correlate with hepatic steatosis, but there is not yet standardization for clinically appropriate cut-offs to determine NAFLD [10]. Moreover, approximately one in four children biopsied for suspected NAFLD may have an alternate liver diagnosis [8]. Thus, in order to properly evaluate the results of a specific intervention for NAFLD, it is important to assure that all children participating do in fact have NAFLD.

There were two studies of dietary intervention in children with hepatic steatosis detected by magnetic resonance spectroscopy (MRS) via Hepatic Fat Fraction (HFF). Ramon-Krauel et al studied 17 obese children with HFF > 9% at baseline. Participants were randomly assigned to either a low-glycemic diet, emphasizing a selection of carbohydrate-containing foods with a low to moderate glycemic load, or a low-fat diet, which was based on limiting total fat to <30% of total calories and saturated fat to <10%, for a 6-month period. Children assigned to low-glycemic diet lost an average of 0.7 kg from baseline while the low-fat group lost an average of 1.5 kg with no significant difference between groups. Both the low-glycemic and low-fat diets had significant decreases in ALT from baseline, –29 U/L for the low-glycemic group and –18 U/L for the low-fat group, though there was no significant difference between the groups. Both diet groups had significant decreases in HFF, from 23.8% at baseline to 15.4% for the low-glycemic group, and 29.3% to 18.7% for the low-fat group with no significant difference between the two groups. There was no significant difference in change of HFF or ALT between the two groups [11].

Jin et al investigated the effect of fructose reduction on overweight and obese children with hepatic fat fraction of >8% measured by MRS. In this study, 24 overweight adolescents that consumed at least 3 sugar sweetened beverages per day were randomly assigned to consume 3 servings (8oz each) of either glucose-containing beverages or fructose-containing beverages per day over a 4-week period. There was no significant change in hepatic fat fraction, body weight, or ALT in either group from baseline [12].

EXERCISE

General Recommendations

For all children, the NHLBI recommends moderate physical activity for 1 hour per day with vigorous exercise 3 days per week along with limiting screen time to no more than 2 hours per day. According to the 2008 physical activity guidelines by the US Department of Health and Human Services, children should have 60 minutes of physical activity every day. In addition, children should have vigorous-intensity physical activity for 3 days of the week, muscle-strengthening physical activity for 3 days of the week, and bone-strengthening physical activity for 3 days of the week [13].

Basis for Recommendations in NAFLD

Exercise is a universally recommended intervention in the treatment of NAFLD in children. There are data in adults that suggest that exercise can be beneficial for NAFLD without dietary change and without weight loss [14–17]. Studies of exercise alone as a therapy alone in NAFLD in children are extremely limited. Furthermore, there have been no studies that have investigated exercise as a treatment for children with biopsy-proven NAFLD. The available studies investigated the effect of exercise in obese children as the target population and all but one measured change in HFF by MRS.

Lee et al investigated the effect of aerobic and resistance exercise versus control in obese children, with one study in boys and one in girls. Each study had 44 children. The aerobic intervention was comprised of three sessions per week, 60 minutes per session with treadmill, elliptical, or stationary bike. The resistance intervention was comprised of 10 whole-body exercises three times per week for 60 minutes per session. The investigators reported changes in HFF for the groups overall. However, very few children had sufficient liver fat to have been considered as having NAFLD; there were 12 boys and 5 girls with HFF > 5.0%. Furthermore, the mean HFF at baseline was only 3.3% in boys and 2.3% in girls. The investigators did report a statistically significant change in HFF in the aerobic group in both boys and girls compared to control, -1.9 vs 0.9% ($p=0.05$) and -1.7 vs 0.8% , respectively. In addition, there was a significant change in HFF in the resistance group for boys, -2.0 vs 0.9% . However, whether these small changes in group mean HFF are clinically relevant for those children with NAFLD remains unknown [18,19].

Van der Heijden and colleagues also performed separate studies on the effect of aerobic and resistance exercise in children. In the study of aerobic exercise, 15 obese and 14 lean children were provided a 30-minute intervention twice a week for 12 weeks. For these 29 children overall there was a decrease in the mean HFF from 9% to 6% but no significant change in mean ALT, from a baseline of 39 U/L [20]. In the study of resistance training, 12 obese Hispanic adolescents performed a 1 hour session twice a week for 12 weeks. 7 out of the 12 adolescents had HFF of >5.6%; there was no significant change in HFF. No data were provided for ALT at baseline or in response to the intervention [21].

COMBINATION OF NUTRITION AND EXERCISE

The majority of studies of lifestyle therapy applied a combination of nutrition and exercise. In 1994, Vajro et al first suggested that ALT can improve in obese children with elevated liver chemistry in response to a combined program of nutrition and exercise [22]. Only one such trial was performed in children with biopsy-proven NAFLD. Nobili et al reported an uncontrolled one-year study of 84 children with NAFLD. All children were instructed to follow a balanced, reduced calorie diet and perform moderate intensity exercise for 30 to 45 minutes on 3 days per week. At the conclusion of 1 year, 32% of children had been lost to follow-up. In the remaining 57 children, there was a significant decrease in the mean weight from 60.9 kg to 56 kg and a significant decrease in the mean ALT from 62 U/L to 33 U/L [23].

Koot et al performed a randomized, controlled trial in 51 severely obese children ages 8–18 years old with hepatic steatosis defined as a HFF of >5% by MRS. The intervention of interest was an inpatient lifestyle intervention. Participants were randomly assigned to one of four treatments: 1) long inpatient intervention (six months of inpatient treatment on working days), 2) short inpatient intervention (two months of inpatient treatment followed by four months of biweekly return visits), 3) ambulatory intervention (16 days of ambulatory visits at increasing time-intervals over a 6-month period), or 4) usual care group. The primary treatment goal was normalization of liver fat, which was achieved in only a minority of participants in any group. There was significantly greater rate of achieving the outcome in relation to the intensity of the intervention (inpatient 43%, ambulatory 33%, usual care 22%). A similar trend was seen for normalization of ALT (inpatient 41%, ambulatory 33%, usual care 6%) [24].

Pozzato et al performed an uncontrolled trial in 26 obese children, 9 of whom had hepatic steatosis determined by MRS (HFF = 9%). The intervention was 1 hour of nutritional counseling with written guidelines and moderate exercise of 30–45 min per day for 1 year. Among the 9 children with HFF = 9% at baseline, 7 had a decrease in HFF to below 9%, decreasing from a mean of 18.7% to 1.3%. There was not a significant decrease in ALT, however, the mean ALT at baseline was relatively low, 31 U/L [25].

Many studies were performed in children with suspected NAFLD based upon measurement of ALT and/or abdominal ultrasound. Wang et al performed a randomized controlled trial (RCT) in China of 76 obese children age 10 to 17 years with elevated ALT and evidence of hepatic steatosis by ultrasound. These children were randomly assigned to one of three groups: 1) residential summer camp; 2) usual care; or 3) usual care plus 100 IU/day of vitamin E. The intervention was for a duration of one month. At the camp, children were provided a reduced calorie diet and daily unstructured aerobic exercise. The group at camp had a significant decrease in BMI from 29.1 kg/m² to 27.2 kg/m² (p<0.05) and a significant decrease of mean ALT from 152 to 64 (p<0.05). There was no significant improvement in the usual care groups relative to the lifestyle intervention [26].

In Cincinnati, Ohio, DeVore and colleagues reported on 83 children seen in a dedicated fatty liver clinic with chronic elevation of ALT > 45 U/L. All children were recommended to meet

with a pediatric gastroenterologist and a registered dietitian once every 3 months for counseling on nutrition and exercise. Liver biopsy was performed to establish a diagnosis in 24 children. Notably, children that had a liver biopsy were nearly twice as likely to continue with gastroenterology care for 1 year (71%) than those children who did not have a liver biopsy for diagnosis (37%). For those children who continued to be followed for 1 year, there was a decrease in serum ALT and stabilization of BMI z-score [27].

In Japan, an uncontrolled trial of lifestyle intervention was performed in 73 obese children age 6–14 with elevated ALT (ALT ≥ 30). Children were instructed to exercise and to decrease their portion sizes by 20% for a duration of 3 months. Weight loss was observed in 36 out of 73 children and in 10 children the weight loss was $> 5\%$ of body weight. Normalization of ALT was observed in 20/73 (27%) of participants [28].

In Denmark, Grønbaek et al performed an uncontrolled trial of weight loss in obese children via a 10-week weight loss camp. During the camp, children were provided with healthy low fat ($<24\%$ of caloric intake from fat) food and had 1 hour of moderate intensity exercise daily. The study included 117 obese children, most of whom did not have NAFLD or suspected NAFLD at entry. For the group overall, there was an approximately 10% weight loss. Based upon liver ultrasound, there was hepatic steatosis in 43% at baseline and 31% following the weight loss intervention. In addition, it was reported that 50% of the children had ALT >25 U/L at baseline, and all were noted to have some unspecified decrease in ALT after the 10-week intervention [29].

In Brazil, Campos et al performed an uncontrolled trial in 53 post-pubertal obese adolescents. The intervention included nutritional counseling once a week, and 3 sessions per week of a combination exercise program that included 30 minutes of aerobic and 30 minutes of resistance training. Psychological counseling was also provided as needed. The treatment duration was one year. Of the 53 adolescents who began the intervention, 13 of them dropped out. Out of the remaining 40 adolescents, based upon liver ultrasound, NAFLD was suspected in 45% of children at baseline. After one year, mean ALT decreased from 29 U/L to 24 U/L [30].

Two studies included in this review of combined lifestyle intervention did not have their primary aims focus on hepatic changes, but rather vascular changes. However, they both included hepatic outcomes as part of their studies. In the first study, Pacifico et al reported an uncontrolled study of the effect of lifestyle intervention on vascular flow parameters. The nutrition intervention included a dietary prescription for a hypocaloric diet (25–30 calories/kg/day) with 50–60% carbohydrates, 23–30% fats, and 15–20% protein. The exercise intervention was moderate intensity activity 60 minutes per day for 5 days per week. They enrolled 135 children with suspected hepatic steatosis based upon liver ultrasound. The program was completed by 89% of children (120/135) who had a mean weight loss of -2.0 kg and a decrease in mean ALT from 54 U/L to 37 U/L. In addition, in 38% of children (52/135) liver MRS was performed to assess HFF which decreased from a mean of 15.2% at baseline to 6.4% at 1 year [31].

In the second study, Sanches et al also investigated the effect of a one-year lifestyle intervention on vascular flow parameters. The therapeutic regimen included 1 hour per week of nutritional counseling, 1 hour per week of psychological counseling, and 1 hour per week of physical therapy, along with a 1 hour combined aerobic and resistance exercise program 3 times per week. The study included 131 adolescents age 15–19 of whom 25% had suspected hepatic steatosis based upon liver ultrasound. There were 79 participants who completed the study and had a decrease in mean BMI from 39.5 kg/m² to 34.6 kg/m². They also reported that mean ALT decreased from 27 U/L to 21 U/L [32].

DIETARY SUPPLEMENTS

The US Food and Drug Administration (FDA) notes that, “a dietary supplement is a product intended for ingestion that contains a "dietary ingredient" intended to add further nutritional value to (supplement) the diet” [33]. Potential medical therapies in the form of supplements that have tested in children for NAFLD include vitamin E, omega-3 fatty acids, and probiotics.

Vitamin E

Potential etiologic mechanisms for NAFLD include mitochondrial dysfunction and damage from reactive oxygen species; thus antioxidants, such as vitamin E, have been tested as treatments for NAFLD. The use of vitamin E for the treatment of NAFLD was first proposed by Lavine, who performed a pilot study in 11 children with elevated serum ALT and ultrasound evidence of hepatic steatosis [34]. Subsequently, there have been four studies that investigated Vitamin E, two of which had children with biopsy-proven NAFLD. Vitamin E can be dosed in international units (IU) or mg, and in order to convert between these two, one must know the form of vitamin E that was used. Because most studies did not report the form of vitamin E used, the dosing is reported in IU or mg as stated in the respective study. The Treatment of NAFLD in Children (TONIC) trial was designed with a primary outcome of sustained reduction in ALT for 96 weeks of treatment. In this study, 58 children were randomized to take 400 IU of vitamin E twice a day for 2 years, and 58 children were randomized to placebo. There was no significant effect of vitamin E on serum ALT; 26% of the children taking vitamin E had sustained reduction of ALT compared to 17% of children in the control group. Liver biopsy was repeated after 2 years of therapy in 87% of the children. There was a significant improvement in hepatocyte ballooning, 38% of the vitamin E group had improvement versus 17% of the control group. There was no significant improvement in steatosis, lobular inflammation, portal inflammation, or fibrosis for children taking vitamin E compare to placebo [35].

Nobili and colleagues studied the effect of vitamin E and vitamin C on serum ALT in 88 children with biopsy-proven NAFLD. Children were randomized to receive a combination of vitamin E 600 IU/day and vitamin C 500 mg/day or placebo for 12 months. Children in both groups were also counseled to follow a balanced, hypocaloric diet. After 12 months of intervention, there was no significant difference in normalization of ALT for children receiving combination of vitamins E and C versus placebo (38% treatment group vs. 31% placebo group) [36].

Vajro et al investigated the effect of vitamin E on decreasing serum ALT in 28 children with suspected NAFLD based upon the combination of serum ALT > 60 U/L and obesity. Children were randomized to receive either vitamin E (400 mg/day for 2 months, then vitamin E 100 mg/day for 3 months) or placebo. After 5 months, there was no significant difference in change in ALT between the vitamin E group and placebo [37].

In the vitamin E arm of the study by Wang et al, children received 100 mg/day of vitamin E in addition to usual care at home. These children were compared to those receiving usual care only. In children receiving vitamin E, ALT improved significantly more than children receiving usual care, but this was less than the improvement seen for children who participated in the summer camp lifestyle program [26].

Omega-3 Fatty Acids

Omega-3 fatty acids are polyunsaturated fatty acids that are thought to regulate transcription factors related to hepatic lipid metabolism, leading to increased fatty acid oxidation and down-regulation of pro-inflammatory genes. These include linolenic acid, which are found in plant oils, along with docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), both found in fish oils. Supplementation with omega-3 fatty acids has been investigated as a treatment of NAFLD in children in three studies; two studies used DHA alone and one used a combination of DHA and EPA.

Nobili et al investigated the effect of 6 months of DHA supplementation in children with biopsy-proven NAFLD. In this study, 60 children were randomized to take either 250 mg of DHA or 500 mg of DHA or placebo orally once a day. There was no significant change in weight or ALT in any of the groups. The authors reported an improvement in the appearance of the liver by ultrasound for those receiving DHA compared to placebo [38].

In a second report, Nobili and colleagues followed the 20 children in the DHA 250 mg/day arm for an additional 12 months. For these children, after a total of 18 months, there was an increase in the mean weight from 57.1 kg to 59.8 kg and a significant decrease in mean ALT from 65 to 39 U/L. Liver biopsies were performed and improvements in steatosis, lobular inflammation, and ballooning were noted [39].

Pacifico et al investigated the effect of 6 months of DHA on liver fat in 58 children with biopsy-proven NAFLD. Participants were randomly assigned to receive either 250 mg/day of DHA or placebo. The primary outcome was change in HFF measured by MRS, which decreased significantly more in the group receiving DHA versus placebo (14.0% to 6.5% vs 15.5% to 12.0%). Serum ALT also decreased significantly in the DHA group, but this was not different when compared to placebo [40].

Janczyk et al investigated the effect of 24 weeks of omega-3 fatty acids on serum ALT in a mixed population of 76 children with either biopsy-proven NAFLD or suspected hepatic steatosis based upon ultrasound. Children were randomized to receive either fish oil containing omega-3 long-chain polyunsaturated fatty acids (LC-PUFA) (DHA and EPA [EPA in a 3:2 proportion 450–1300 mg/day]) or placebo (sunflower oil, containing omega-6 LC-PUFA). The dose of omega-3 fatty acids was determined by baseline weight (<40 kg –

450 mg/day, 40–60 kg – 900 mg/day, >60 kg – 1300 mg/day). In addition, children met with an experienced dietitian in order to promote weight loss of 0.5 kg per week using an individualized diet plan and increased physical activity. Only the omega-3 group had a significant decrease in BMI. There was no significant improvement in ALT with omega-3 fatty acid supplementation [41].

Probiotics

Disturbance of the gut-liver axis is also believed to play a role in the development of NAFLD through changes such as small intestinal bacterial overgrowth, increased intestinal permeability, and intestinal dysbiosis. The potential for probiotics to correct these abnormalities has led to enthusiasm that probiotics may be beneficial for NAFLD. In children, there have been two such studies, one with *Lactobacillus*, a single-strain preparation, and the other with VSL#3, a proprietary multi-strain blend.

Vajro et al studied the effect of 8 weeks of *Lactobacillus rhamnosus* in 20 obese children with elevated ALT and suspected hepatic steatosis evaluated by ultrasound. The children were randomized to receive 12 billion colony forming units (CFU) per day of *Lactobacillus* or placebo. Children taking *Lactobacillus* had a significant improvement in serum ALT compared to those who received placebo (70 to 40 U/L vs 64 to 61 U/L) [42].

In a study by Alisi et al, 48 obese children with biopsy-proven NAFLD were given 1 sachet per day of VSL#3 or placebo for 4 months. The authors proposed a new ultrasound probability score and report that the score improved in the VSL#3 group compared to the control group. The authors also noted that ALT did not improve with VSL#3 treatment [43].

DISCUSSION

We performed a review of lifestyle interventions including diet and exercise for children with NAFLD. Because dietary supplements are often included in lifestyle treatment programs, we also reviewed the extant literature of clinical trials utilizing dietary supplements for pediatric NAFLD. Studies of diet alone did not indicate any one dietary approach that was superior to another for the treatment of pediatric NAFLD. Studies of exercise alone were performed in obese children, many of whom did not have NAFLD, but suggested that exercise may improve hepatic steatosis. Studies of the combination of diet and exercise suggested a potential for improvement in serum ALT and/or MRI with intervention. Dietary supplements were reported to have inconsistent effects on NAFLD in children.

Studying treatments for NAFLD in children is complicated by issues related to diagnosis, disease heterogeneity, and appropriate tools for and choice of outcome. One such challenge is knowing if the intervention is being applied to the correct population. An accurate diagnosis of NAFLD requires a combination of clinical history, detailed laboratory investigation, and review of liver histology [44]. Reliance on serum ALT or liver ultrasonography is likely to include children without liver disease as well as children with liver conditions other than NAFLD [8,9]. Furthermore, NAFLD in children has several histologic subtypes which may represent different underlying pathophysiology, and thus

even different diseases [45]. Because of such heterogeneity, there also may be differences in response to therapies across the spectrum of NAFLD in children. An additional challenge is the choice of outcome to measure. Studies are more easily done using non-invasive measures, such as ALT or HFF, but it is unclear how well changes in these parameters reflect changes in liver histology. Moreover, the amount of change in any given histologic parameter that is most relevant to improvement in long-term outcomes for children is not known. These challenges have impacted studies of lifestyle intervention and dietary supplements to date, and must be addressed in order to further advance the evidence base for the treatment of pediatric NAFLD.

Studies of diet alone in the treatment of pediatric NAFLD have focused on sugar and carbohydrate. The role of fructose in the pathophysiology of NAFLD remains interesting and controversial [46–48]. It is thought that fructose plays a role in *de novo* lipogenesis, which may be a critical contributor to the development of NAFLD. It is also possible that other monosaccharides and disaccharides play a role in the development of NAFLD when added to the diet. Notably, a low fat diet was equally effective as a low glycemic index diet in decreasing hepatic steatosis. In part, the confusion regarding the role of sugars and carbohydrates versus fats is confounded by the role of obesity in pediatric NAFLD. For children who are obese and have NAFLD, weight loss may have a beneficial effect regardless of the diet used. It is unknown to what extent any specific diet may benefit the liver directly, independent of the effect of body weight. Because substantial weight loss is difficult to achieve, it is important to know whether diet can be useful for treating NAFLD without requiring weight loss. If this were proven to be true, it would reshape clinical goal setting for children with NAFLD. In addition, some children with NAFLD are normal weight and thus weight loss is not indicated.

Exercise is widely believed to improve NAFLD because a sedentary lifestyle, poor aerobic fitness, and low muscle mass are all risk factors for NAFLD [49–53]. As such, guidelines recommend exercise as a primary form of treatment for NAFLD [5]. However, the guidelines do not provide any specifics for the prescription of exercise. This is because there is insufficient evidence regarding the efficacy of exercise as a treatment for NAFLD. To date, there have been no RCTs of exercise as a treatment for children with NAFLD. Multiple pediatric trials have treated obesity with exercise, however most of the children in these studies did not have NAFLD. These studies suggest that liver fat can decrease in the context of exercise, however, the effect of exercise in children with NAFLD, who typically have liver fat fractions between 10 and 35% cannot be extrapolated from these studies. Moreover, most studies did not evaluate ALT, which is the most common measure in the evaluation and management of NAFLD. Thus, rigorous studies of structured exercise as a treatment for children with biopsy-proven NAFLD should be a high priority.

Recommendations for lifestyle interventions include both dietary and exercise components. Therefore, most studies have included multi-modal interventions. Studies of combination lifestyle interventions relevant to pediatric NAFLD have included a total of 832 children of whom 59% were known or suspected to have NAFLD [22–32]. Moreover, only 65% of participants completed the recommended interventions. Study duration ranged from 4 weeks to 52 weeks. Some children in these studies had normalization of ALT or MRI hepatic fat

fraction. Thus, one can anticipate a decrease in ALT and liver fat if a child receives moderate to intensive counseling and support, follows recommendations, and follows up on a regular basis. However, the nature of differences in inclusion criteria, intervention, duration of treatment, and outcomes measured makes it impossible to generalize about the effect of any specific lifestyle intervention on the liver and liver-related outcomes for pediatric NAFLD.

There is great enthusiasm for the use of dietary supplements as complementary and alternative medicine. Studies in children have shown inconsistent effects of vitamin E, fish oil, and probiotics. Moreover, no supplement has been shown to benefit a majority of children with NAFLD. The effect of vitamin E appears to be limited to improvement in ballooning in a minority of children who take it. Additionally, taking vitamin E supplements has been shown to prevent health-promoting effects of physical exercise [54]. Moreover, in adults who consume treatment doses of vitamin E, there is a potential for increased risk of cardiovascular disease and cancer [55–57]. Thus, the decision to use vitamin E for any individual patient requires a careful risk versus benefit analysis. An important lesson can also be learned from the arc of enthusiasm for fish oil in the prevention of cardiovascular disease in adults. In the United States, over 1 billion dollars is spent on fish oil annually [58]. This is despite high quality studies disproving any role in the prevention of myocardial infarction or stroke [59,60]. In addition, studies of fish oil in adults with NASH has been disappointing with one study showing no benefit and a second study shown worsening of insulin resistance [61,62]. Due to the small numbers of children with NAFLD treated to date and the concerns raised by larger studies in adults, omega 3 fatty acids should still be considered experimental for children with NAFLD. Similarly, due to the increasing data suggesting a role for the microbiome in the development of NAFLD, there is excitement about probiotics as potential therapy for children with NAFLD. Studies to date support a need for additional clinical trials to be done. However, the need for investigational new drug approval by the FDA in order to properly test a probiotic as a therapy for a disease such as NAFLD has been an important stumbling block [63]. Clinicians should insist that studies of dietary supplements follow the same rigor as studies of medications before they recommend them to children with NAFLD.

Children with NAFLD may have a distinct physiology that is different from obesity alone and has the potential to influence lifestyle treatments. The majority of children who are obese do not have NAFLD [1]. Moreover, not all children with NAFLD are obese [1,64]. When compared to peers matched for age, sex, and BMI, children with NAFLD are much more likely to have insulin resistance, dyslipidemia, and hypertension [65,66]. After controlling for obesity, these alterations can cause harm in adolescents such that those with NAFLD, and are also more likely to have abnormal cardiac physiology including left ventricular dysfunction compared to adolescents without NAFLD [67–70]. In addition to altered physiology, children with NAFLD are more likely to have impaired quality of life and anxiety than matched peers [71]. Thus the physiological and psychological status of children with NAFLD may impact the ability to initiate changes as well as hinder the response to these changes.

In conclusion, there is a lack of randomized controlled trials with evidence that show that lifestyle interventions or supplements are effective for the treatment of NAFLD, and there is

a need for large randomized controlled trials that investigate specific dietary interventions and exercise regimens with the goal to have specific evidence-based recommendations for the treatment of NAFLD.

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REFERENCES

1. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. *Pediatrics*. 2006; 118:1388–1393. [PubMed: 17015527]
2. Molleston JP, Schwimmer JB, Yates KP, Murray KF, Cummings OW, Lavine JE, et al. Histological abnormalities in children with nonalcoholic fatty liver disease and normal or mildly elevated alanine aminotransferase levels. *J. Pediatr*. 2014; 164:707–713.e3. [PubMed: 24360992]
3. Feldstein AE, Charatcharoenwithaya 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; 58:1538–1544. [PubMed: 19625277]
4. Nobili V, Alisi A, Grimaldi C, Liccardo D, Francalanci P, Monti L, et al. Non-alcoholic fatty liver disease and hepatocellular carcinoma in a 7-year-old obese boy: coincidence or comorbidity? *Pediatr. Obes*. 2013:1–4.
5. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology*. 2012; 142:1592–1609. [PubMed: 22656328]
6. Gidding SS, Lichtenstein AH, Faith MS, Karpyn A, Mennella JA, Popkin B, et al. Implementing American Heart Association Pediatric and Adult Nutrition Guidelines: A Scientific Statement From the American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular Disease. *Circulation*. 2009; 119:1161–1175. [PubMed: 19255356]
7. Daniels, Tephner, Benue, Irwin, Christakis, Da, Dennison, Ba. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Expert Panel Integr. Guidel. Cardiovasc. Heal. Risk Reduct. Child. Adolesc*. 2012; 216
8. Schwimmer JB, Newton KP, Awai HI, Choi LJ, Garcia Ma, Ellis LL, et al. Paediatric gastroenterology evaluation of overweight and obese children referred from primary care for suspected non-alcoholic fatty liver disease. *Aliment. Pharmacol. Ther*. 2013; 38:1267–1277. [PubMed: 24117728]
9. Awai HI, Newton KP, Sirlin CB, Behling C, Schwimmer JB. Evidence and Recommendations for Imaging Liver Fat in Children, Based on Systematic Review. *Clin. Gastroenterol. Hepatol*. 2014; 12:765–773. [PubMed: 24090729]
10. Schwimmer JB, Middleton MS, Behling C, Newton KP, Awai HI, Paiz MN, et al. Magnetic resonance imaging and liver histology as biomarkers of hepatic steatosis in children with nonalcoholic fatty liver disease. *Hepatology*. 2015 n/a–n/a.
11. Ramon-Krauel M, Salsberg SL, Ebbeling CB, Voss SD, Mulkern RV, Apura MM, et al. A low-glycemic-load versus low-fat diet in the treatment of fatty liver in obese children. *Child. Obes*. 2013; 9:252–260. [PubMed: 23705885]
12. Jin R, Welsh JA, Le N-A, Holzberg J, Sharma P, Martin DR, et al. Dietary fructose reduction improves markers of cardiovascular disease risk in Hispanic-American adolescents with NAFLD. *Nutrients*. 2014; 6:3187–3201. [PubMed: 25111123]

13. Services UD of H and H. 2008 Physical Activity Guidelines for Americans. 2008. www.health.gov/paguidelines
14. Hallsworth K, Fattakhova G, Hollingsworth KG, Thoma C, Moore S, Taylor R, et al. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. *Gut*. 2011; 60:1278–1283. [PubMed: 21708823]
15. Johnson, Na; Sachinwalla, T.; Walton, DW.; Smith, K.; Armstrong, A.; Thompson, MW., et al. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. *Hepatology*. 2009; 50:1105–1112. [PubMed: 19637289]
16. Bacchi E, Negri C, Targher G, Faccioli N, Lanza M, Zoppini G, et al. Both resistance training and aerobic training reduce hepatic fat content in type 2 diabetic subjects with nonalcoholic fatty liver disease (the RAED2 Randomized Trial). *Hepatology*. 2013; 58:1287–1295. [PubMed: 23504926]
17. Bacchi E, Negri C, Zanolin ME, Milanese C, Faccioli N, Trombetta M, et al. Metabolic effects of aerobic training and resistance training in type 2 diabetic subjects: a randomized controlled trial (the RAED2 study). *Diabetes Care*. 2012; 35:676–682. [PubMed: 22344613]
18. Lee S, Deldin AR, White D, Kim Y, Libman I, Rivera-Vega M, et al. Aerobic exercise but not resistance exercise reduces intrahepatic lipid content and visceral fat and improves insulin sensitivity in obese adolescent girls: a randomized controlled trial. *Am. J. Physiol. Endocrinol. Metab*. 2013; 305:E1222–E1229. [PubMed: 24045865]
19. Lee S, Bacha F, Hannon T, Kuk JL, Boesch C, Arslanian S. Effects of aerobic versus resistance exercise without caloric restriction on abdominal fat, intrahepatic lipid, and insulin sensitivity in obese adolescent boys: a randomized, controlled trial. *Diabetes*. 2012; 61:2787–2795. [PubMed: 22751691]
20. van der Heijden G-J, Wang ZJ, Chu ZD, Sauer PJJ, Haymond MW, Rodriguez LM, et al. A 12-week aerobic exercise program reduces hepatic fat accumulation and insulin resistance in obese, Hispanic adolescents. *Obesity (Silver Spring)*. 2010; 18:384–390. [PubMed: 19696755]
21. van der Heijden G-J, Wang ZJ, Chu Z, Toffolo G, Manesso E, Sauer PJJ, et al. Strength Exercise Improves Muscle Mass and Hepatic Insulin Sensitivity in Obese Youth. *Med. Sci. Sport. Exerc*. 2010; 42:1973–1980.
22. Vajro P, Fontanella a, Perna C, Orso G, Tedesco M, De Vincenzo a. Persistent hyperaminotransferasemia resolving after weight reduction in obese children. *J. Pediatr*. 1994; 125:239–241. [PubMed: 8040771]
23. Nobili V, Marcellini M, Devito R, Ciampalini P, Piemonte F, Comparcola D, et al. NAFLD in children: A prospective clinical-pathological study and effect of lifestyle advice. *Hepatology*. 2006; 44:458–465. [PubMed: 16871574]
24. Koot BGP, van der Baan-Slootweg OH, Vinke S, Bohte AE, Tamminga-Smeulders CLJ, Jansen PLM, et al. Intensive lifestyle treatment for non-alcoholic fatty liver disease in children with severe obesity: inpatient versus ambulatory treatment. *Int. J. Obes*. 2015:1–33.
25. Pozzato C, Verduci E, Scaglioni S, Radaelli G, Salvioni M, Rovere A, et al. Liver Fat Change in Obese Children After a 1-year Nutrition-behavior Intervention. *J. Pediatr. Gastroenterol. Nutr*. 2010; 51:1. [PubMed: 20543717]
26. Wang C-L, Liang L, Fu J-F, Zou C-C, Hong F, Xue J-Z, et al. Effect of lifestyle intervention on non-alcoholic fatty liver disease in Chinese obese children. *World J. Gastroenterol*. 2008; 14:1598–1602. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2693759&tool=pmcentrez&rendertype=abstract>. [PubMed: 18330955]
27. DeVore S, Kohli R, Lake K, Nicholas L, Dietrich K, Balistreri WF, et al. A Multidisciplinary Clinical Program Is Effective in Stabilizing BMI and Reducing Transaminase Levels in Pediatric Patients With NAFLD. *J. Pediatr. Gastroenterol. Nutr*. 2013; 57:119–123. [PubMed: 23518484]
28. Tazawa Y, Noguchi H, Nishinomiya F, Takada G. Effect of weight reduction on serum transaminase activities in children with simple obesity. *J. Pediatr*. 1996; 128:587–588. [PubMed: 8618202]
29. Grønbaek H, Lange A, Birkebæk NH, Holland-Fischer P, Solvig J, Hørlyck A, et al. Effect of a 10-week weight loss camp on fatty liver disease and insulin sensitivity in obese Danish children. *J. Pediatr. Gastroenterol. Nutr*. 2012; 54:223–228. [PubMed: 21760546]

30. Campos RMS, De Piano A, Da Silva PL, Carnier J, Sanches PL, Corgosinho FC, et al. The role of pro/anti-inflammatory adipokines on bone metabolism in NAFLD obese adolescents: Effects of long-term interdisciplinary therapy. *Endocrine*. 2012; 42:146–156. [PubMed: 22315014]
31. Pacifico L, Arca M, Anania C, Cantisani V, Di Martino M, Chiesa C. Arterial function and structure after a 1-year lifestyle intervention in children with nonalcoholic fatty liver disease. *Nutr. Metab. Cardiovasc. Dis*. 2013; 23:1010–1016. [PubMed: 23018041]
32. Sanches PL, de Piano A, Campos RMS, Carnier J, de Mello MT, Elias N, et al. Association of nonalcoholic fatty liver disease with cardiovascular risk factors in obese adolescents: The role of interdisciplinary therapy. *J. Clin. Lipidol*. 2014; 8:265–272. [PubMed: 24793347]
33. Nutrition C for FS and A. [accessed December 21, 2015] FDA Basics - What is a dietary supplement?. n.d.; <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm195635.htm>
34. Lavine JE. Vitamin E treatment of nonalcoholic steatohepatitis in children: a pilot study. *J. Pediatr*. 2000; 136:734–738. [PubMed: 10839868]
35. Lavine JE, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. *JAMA*. 2011; 305:1659–1668. [PubMed: 21521847]
36. Nobili V, Manco M, Devito R, Ciampalini P, Piemonte F, Marcellini M. Effect of vitamin E on aminotransferase levels and insulin resistance in children with non-alcoholic fatty liver disease. *Aliment. Pharmacol. Ther*. 2006; 24:1553–1561. [PubMed: 17206944]
37. Vajro P, Mandato C, Franzese A, Ciccimarra E, Lucariello S, Savoia M, et al. Vitamin E treatment in pediatric obesity-related liver disease: a randomized study. *J. Pediatr. Gastroenterol. Nutr*. 2004; 38:48–55. [PubMed: 14676594]
38. Nobili V, Bedogni G, Alisi A, Pietrobattista A, Risé P, Galli C, et al. Docosahexaenoic acid supplementation decreases liver fat content in children with non-alcoholic fatty liver disease: double-blind randomised controlled clinical trial. *Arch. Dis. Child*. 2011; 96:350–353. [PubMed: 21233083]
39. Nobili V, Carpino G, Alisi A, De Vito R, Franchitto A, Alpini G, et al. Role of Docosahexaenoic Acid Treatment in Improving Liver Histology in Pediatric Nonalcoholic Fatty Liver Disease. *PLoS One*. 2014; 9:e88005. [PubMed: 24505350]
40. Pacifico L, Bonci E, Di Martino M, Versacci P, Andreoli G, Silvestri LM, et al. A double-blind, placebo-controlled randomized trial to evaluate the efficacy of docosahexaenoic acid supplementation on hepatic fat and associated cardiovascular risk factors in overweight children with nonalcoholic fatty liver disease. *Nutr. Metab. Cardiovasc. Dis*. 2015; 25:734–741. [PubMed: 26026214]
41. Janczyk W, Lebensztejn D, Wierzbicka-Rucinska A, Mazur A, Neuhoff-Murawska J, Matusik P, et al. Omega-3 Fatty acids therapy in children with nonalcoholic Fatty liver disease: a randomized controlled trial. *J. Pediatr*. 2015; 166:1358–1363.e3. [PubMed: 25771388]
42. Vajro P, Mandato C, Licenziati MR, Franzese A, Vitale DF, Lenta S, et al. Effects of *Lactobacillus rhamnosus* strain GG in pediatric obesity-related liver disease. *J. Pediatr. Gastroenterol. Nutr*. 2011; 52:740–743. [PubMed: 21505361]
43. Alisi, a; Bedogni, G.; Baviera, G.; Giorgio, V.; Porro, E.; Paris, C., et al. Randomised clinical trial: the beneficial effects of VSL#3 in obese children with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther*. 2014
44. Schwimmer JB. Definitive diagnosis and assessment of risk for nonalcoholic fatty liver disease in children and adolescents. *Semin. Liver Dis*. 2007; 27:312–318. [PubMed: 17682977]
45. Schwimmer JB, Behling C, Newbury R, Deutsch R, Nievergelt C, Schork NJ, et al. Histopathology of pediatric nonalcoholic fatty liver disease. *Hepatology*. 2005; 42:641–649. [PubMed: 16116629]
46. Ouyang X, Cirillo P, Sautin Y, McCall S, Bruchette JL, Diehl AM, et al. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. *J. Hepatol*. 2008; 48:993–999. [PubMed: 18395287]
47. O'sullivan, Ta; Oddy, WH.; Bremner, AP.; Sherriff, JL.; Ayonrinde, OT.; Olynyk, JK., et al. Lower fructose intake may help protect against development of nonalcoholic Fatty liver in adolescents with obesity. *J. Pediatr. Gastroenterol. Nutr*. 2014; 58:624–631. [PubMed: 24345826]

48. Abdelmalek MF, Suzuki A, Guy C, Unalp-Arida A, Colvin R, Johnson RJ, et al. Increased fructose consumption is associated with fibrosis severity in patients with nonalcoholic fatty liver disease. *Hepatology*. 2010; 51:1961–1971. [PubMed: 20301112]
49. Trikk JL, Ortaglia A, Blair SN, Bottai M, Church TS, Pate RR. Cardiorespiratory fitness, waist circumference, and alanine aminotransferase in youth. *Med. Sci. Sports Exerc.* 2013; 45:722–727. [PubMed: 23190589]
50. Gerber L, Otgonsuren M, Mishra a, Escheik C, Birerdinc a, Stepanova M, et al. Non-alcoholic fatty liver disease (NAFLD) is associated with low level of physical activity: A population-based study. *Aliment. Pharmacol. Ther.* 2012; 36:772–781. [PubMed: 22958053]
51. Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, Webb M, Zvibel I, Goldiner I, et al. Role of leisure-time physical activity in nonalcoholic fatty liver disease: A population-based study. *Hepatology*. 2008; 48:1791–1798. [PubMed: 18972405]
52. Petersen KF, Dufour S, Savage DB, Bilz S, Solomon G, Yonemitsu S, et al. The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. *Proc. Natl. Acad. Sci. U. S. A.* 2007; 104:12587–12594. [PubMed: 17640906]
53. Wittmeier KDM, Wicklow Ba, MacIntosh AC, Sellers EaC, Ryner LN, Serrai H, et al. Hepatic Steatosis and Low Cardiorespiratory Fitness in Youth With Type 2 Diabetes. *Obesity*. 2012; 20:1034–1040. [PubMed: 22222927]
54. Ristow M, Zarse K, Oberbach A, Klötting N, Birringer M, Kiehntopf M, et al. Antioxidants prevent health-promoting effects of physical exercise in humans. *Proc. Natl. Acad. Sci. U. S. A.* 2009; 106:8665–8670. [PubMed: 19433800]
55. Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM, et al. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA J. Am. Med. Assoc.* 2005; 293:1338–1347.
56. Klein, Ea; Thompson, IM.; Tangen, CM.; Crowley, JJ.; Lucia, MS.; Goodman, PJ., et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2011; 306:1549–1556. [PubMed: 21990298]
57. Miller ER, Pastor-Barriuso R, Dalal D, Riemersma Ra, Appel LJ, Guallar E. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Ann. Intern. Med.* 2005; 142:37–46. [PubMed: 15537682]
58. Whoriskey P. Fish oil pills: A \$1.2 billion industry built, so far, on empty promises. *Washington Post*. 2015 https://www.washingtonpost.com/business/economy/claims-that-fish-oil-boosts-health-linger-despite-science-saying-the-opposite/2015/07/08/db7567d2-1848-11e5-bd7f-4611a60dd8e5_story.html?hpid=z4.
59. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA*. 2012; 308:1024–1033. [PubMed: 22968891]
60. Bosch J, Gerstein HC, Dagenais GR, Díaz R, Dyal L, Jung H, et al. N-3 Fatty Acids and Cardiovascular Outcomes in Patients With Dysglycemia. *N. Engl. J. Med.* 2012; 367:309–318. [PubMed: 22686415]
61. Sanyal AJ, Abdelmalek MF, Suzuki A, Cummings OW, Chojkier M. No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. *Gastroenterology*. 2014; 147:377–384.e1. [PubMed: 24818764]
62. Dasarathy S, Dasarathy J, Khyami A, Yerian L, Hawkins C, Sargent R, et al. Double-blind Randomized Placebo-controlled Clinical Trial of Omega 3 Fatty Acids for the Treatment of Diabetic Patients With Nonalcoholic Steatohepatitis. *J. Clin. Gastroenterol.* 2014; 00:1–8.
63. Degnan FH. Clinical studies involving probiotics: when FDA’s investigational new drug rubric applies-and when it may not. *Gut Microbes*. 2012; 3:485–489. [PubMed: 23060015]
64. Pardee PE, Lavine JE, Schwimmer JB. Diagnosis and treatment of pediatric nonalcoholic steatohepatitis and the implications for bariatric surgery. *Semin. Pediatr. Surg.* 2009; 18:144–151. [PubMed: 19573756]
65. Schwimmer JB, Pardee PE, Lavine JE, Blumkin AK, Cook S. Cardiovascular risk factors and the metabolic syndrome in pediatric nonalcoholic fatty liver disease. *Circulation*. 2008; 118:277–283. [PubMed: 18591439]

66. Schwimmer JB, Zepeda A, Newton KP, Xanthakos Sa, Behling C, Hallinan EK, et al. Longitudinal Assessment of High Blood Pressure in Children with Nonalcoholic Fatty Liver Disease. *PLoS One*. 2014; 9:e112569. [PubMed: 25419656]
67. Sert A, Pirgon O, Aypar E, Yilmaz H, Odabas D. Relationship between left ventricular mass and carotid intima media thickness in obese adolescents with non-alcoholic fatty liver disease. *J Pediatr Endocrinol Metab*. 2012; 25:927–934. [PubMed: 23426822]
68. Alp H, Eklioglu BS, Atabek ME, Karaarslan S, Baysal T, Altin H, et al. Evaluation of epicardial adipose tissue, carotid intima-media thickness and ventricular functions in obese children and adolescents. *J. Pediatr. Endocrinol. Metab*. 2014; 25:927–934.
69. Singh GK, Vitola BE, Holland MR, Sekarski T, Patterson BW, Magkos F, et al. Alterations in ventricular structure and function in obese adolescents with nonalcoholic fatty liver disease. *J. Pediatr*. 2013; 162:1160–1168. 1168.e1. [PubMed: 23260104]
70. Pacifico L, Di Martino M, De Merulis A, Bezzi M, Osborn JF, Catalano C, et al. Left ventricular dysfunction in obese children and adolescents with nonalcoholic fatty liver disease. *Hepatology*. 2014; 59:461–470. [PubMed: 23843206]
71. Kistler KD, Molleston J, Unalp a, Abrams SH, Behling C, Schwimmer JB. Symptoms and quality of life in obese children and adolescents with non-alcoholic fatty liver disease. *Aliment. Pharmacol. Ther*. 2010; 31:396–406. [PubMed: 19863497]

Bullet Points

Key Findings

- Lifestyle interventions are uniformly recommended for the treatment of NAFLD in children
- The evidence base for any specific dietary and/or exercise intervention in the treatment of NAFLD in children is limited

Future Unmet Needs

- Rigorous studies of lifestyle interventions as a treatment for children with biopsy-proven NAFLD are an urgent need
- Studies are needed to identify the duration, frequency, and intensity of exercise that yields the optimal benefit for children with NAFLD

Implications for the Clinician

- The clinician should work with the child and family to individualize the lifestyle goals taking into consideration the severity of NAFLD, presence and degree of obesity, and other associated co-morbidities
- Dietary supplements should be considered as experimental with potential risks

Table 1 Studies investigating dietary, exercise, and combined interventions for the treatment of NAFLD in children

| Author | Country | Sample Size | Mean Age (years±SD) | Population | Study Duration | Metric of Improvement | Intervention |
|---|---------|-------------|---------------------|--|----------------|-----------------------|---|
| Nutrition as Monotherapy | | | | | | | |
| Ramon-Krauel 2013 [11] | USA | 17 | 11.8±3.0 | Obese children with MRS HFF 9% | 6 months | Change in HFF | Low-glycemic diet vs low-fat diet |
| Jin 2014 [12] | USA | 24 | 13.5 | Overweight Hispanic children, overweight that consume at least 3 sweet beverages daily | 4 weeks | Change in HFF | Substitute fructose beverages with glucose beverages |
| Exercise as Monotherapy | | | | | | | |
| van der Heijden 2010 [20] | USA | 29 | 15.6±0.4 | Sedentary, Hispanic adolescents, Lean group vs Obese group. | 12 weeks | Change in HFF | Aerobic exercise program (30 min, 4 days per week) |
| van der Heijden 2010 [21] | USA | 12 | 15.5±0.5 | Obese adolescents | 12 weeks | Change in HFF | Resistance exercise program (1 hr, 2 days per week) |
| Lee 2012 [19] | USA | 45 | 14.9 | Inactive, Obese boys | 3 months | Change in HFF | Aerobic vs resistance exercise program |
| Lee 2013 [18] | USA | 44 | 14.8 | Inactive, Obese girls | 3 months | Change in HFF | Aerobic vs resistance exercise program |
| Nutrition and Exercise Multi-modal Therapy | | | | | | | |
| Vajro 1994 [22] | Italy | 9 | 8.7±2.1 | Chronic ALT >40 | 12 months | Change in ALT | Individualized regimen of balanced diet and physical exercise |
| Tazawa 1997 [28] | Japan | 110 | Range: 6–18 yrs | Obese children with persistently elevated | 3 months | Change in ALT | 20% reduction in calories + exercise recommendations |

| Author | Country | Sample Size | Mean Age (years±SD) | Population | Study Duration | Metric of Improvement | Intervention |
|--------------------|---------|-------------|---------------------|--|----------------|---|--|
| Nobili 2006 [13] | Italy | 84 | 11.7±3.3 | LFTs vs those without elevated LFTs Biopsy-proven NAFLD | 1 year | Change in ALT and liver ultrasound appearance | 1-hr nutritional counseling w/ balanced, low-calorie diet; moderate exercise program (30–45 min/day 3×/week) |
| Wang 2008 [26] | China | 76 | 13.7±1.9 | Obese children with abnormal ultrasound and elevated ALT | 1 month | Change in ALT and liver ultrasound appearance | Summer camp with 3 hours aerobic exercise (unstructured), dietary management (low-calorie) for 1 month. |
| Pozzato 2010 [25] | Italy | 26 | Range: 6–14 yrs | Obese children | 1 year | Change in HFF | Recommend balanced diet and active lifestyle |
| Grønbeek 2012 [29] | Denmark | 117 | 12.1±1.3 | Obese children with abnormal ultrasound and elevated ALT | 10 weeks | Change in liver ultrasound appearance | Summer camp with controlled weight-loss diet and moderate to strenuous supervised physical activity |
| Campos 2012 [30] | Brazil | 53 | 17±1.7 | Post-pubertal adolescents | 1 year | Change in ALT | Weekly dietary lessons and exercise 3×/week (30 min aerobic, 30 min resistance) |
| Pacifico 2013 [31] | Italy | 135 | 11.9 | Obese children with abnormal liver ultrasound and elevated ALT | 12 months | Change in BMI z-score, ALT, HFF | Diet and exercise education (60 min/day × 5 days/week) |
| DeVore 2013 [27] | USA | 108 | 14 | Children with ALT >45 | 1 year | Change in BMI z-score, ALT | Dietary and exercise advice every 3 months |

| Author | Country | Sample Size | Mean Age (years±SD) | Population | Study Duration | Metric of Improvement | Intervention |
|-------------------|-------------|-------------|---------------------|---|----------------|------------------------------|--|
| Sanches 2014 [32] | Brazil | 79 | 17±2 | Obese children with abnormal liver ultrasound | 1 year | Change in BMI and ALT | Diet counseling 1×/wk, individual nutrition consult; group behavioral counseling; exercise 3×/week combined 30 aerobic, 30 resistance) |
| Koot 2015 [24] | Netherlands | 80 | 14.7±2.4 | Obese children with HFF > 5% | 6 months | Normalization of HFF and ALT | 4 Treatment groups: 1) inpatient 2) 2 month inpatient 4×/week, then 4 month 2×/week visits for 2 days each, 3) ambulatory, 4) usual care |

Table 2

Studies investigating dietary supplements for the treatment of NAFLD in children

| Author | Country | Sample Size | Mean Age (years±SD) | Population | Duration | Metric of Improvement | Intervention |
|--------------------|---------|-------------|---------------------|---|--------------------------|---|--|
| Vitamin E | | | | | | | |
| Lavine 2000 [34] | USA | 11 | 12.4±1.6 | Obese children with elevated ALT and abnormal liver ultrasound | Variable: 4 to 10 months | ALT normalization | Vitamin E 400–1200 IU/day |
| Vajro 2004 [37] | Italy | 28 | 10.3±3.7 | Children with ALT 1.5 ULN | 5 months | Change in ALT | Vitamin E 400 mg/day, then 100 mg/day |
| Nobili 2006 [36] | Italy | 88 | 12.1±3.2 | Biopsy-proven NAFLD | 12 months | Change in ALT | Vitamin E 600 IU/day, Vitamin C 500 mg/day × 12 months |
| Wang 2008 [26] | China | 76 | 13.7±1.9 | Obese children with abnormal liver ultrasound and ALT 1.5×ULN | 1 month | Change in ALT | Vitamin E 100 mg/day |
| Lavine 2011 [35] | USA | 173 | 13.1±2.4 | Children 8–17 with biopsy-proven NAFLD and chronic ALT >60 U/L | 2 years | Sustained reduction in ALT | Vitamin E 400 IU twice daily |
| Fatty Acids | | | | | | | |
| Nobili 2011 [38] | Italy | 60 | 12 | Biopsy-proven NAFLD | 6 months | Change in ultrasound appearance and ALT | DHA 250mg/day; DHA 500 mg/day |
| Nobili 2014 [39] | Italy | 20 | 10.1±2.0 | Continuation study for children with NAFLD in the DHA 250 mg arm of study #38 | 12 months | Improvement in histology | DHA 250mg/day |
| Pacifico 2015 [40] | Italy | 58 | 10.9 | Biopsy-proven NAFLD | 6 months | Change in HFF | DHA 250 mg/day |

| Author | Country | Sample Size | Mean Age (years±SD) | Population | Duration | Metric of Improvement | Intervention |
|-------------------|---------|-------------|-----------------------------|---|----------|---------------------------------------|--|
| Janczyk 2015 [41] | Poland | 76 | Median 13.0 (IQR 11.1–15.2) | Children with ALT >1.3 ULN and abnormal liver ultrasound | 24 weeks | Decrease in ALT >0.3 times ULN | Omega 3- LC-PUFA (DHA/EPA) 450–1300 mg/day |
| Probiotics | | | | | | | |
| Vairo 2011 [42] | Italy | 20 | 10.7±2.1 | Obese children with ALT >40 and abnormal liver ultrasound | 8 weeks | Change in ALT | Lactobacillus rhamnosus (12 billion CFU/day) |
| Alisi 2014 [43] | Italy | 48 | 10.5 | Obese children with biopsy-proven NAFLD | 4 months | Change in liver ultrasound appearance | VSL #3 1 sachet per day |