





Review

The Role of Macronutrients in the Pathogenesis, Prevention and Treatment of Non-Alcoholic Fatty Liver Disease (NAFLD) in the Paediatric Population—A Review

Thomas Pixner ^{1,2}, Nathalie Stummer ^{2,3}, Anna Maria Schneider ^{2,3} , Andreas Lukas ^{1,2}, Karin Gramlinger ¹, Valérie Julian ⁴ , David Thivel ⁵ , Katharina Mörwald ^{2,3}, Katharina Maruszczak ^{2,3}, Harald Mangge ⁶, Julian Gomahr ^{2,3}, Daniel Weghuber ^{2,3,*}  and Dieter Furthner ^{1,2}

¹ Department of Paediatric and Adolescent Medicine, Salzkammergutklinikum Voecklabruck, 4840 Voecklabruck, Austria; tom.pixner@gmx.at (T.P.); andreas.lukas@oöeg.at (A.L.); karin.gramlinger@oöeg.at (K.G.); dieter.furthner@oöeg.at (D.F.)

² Obesity Research Unit, Paracelsus Medical University, 5020 Salzburg, Austria; nathalie.stummer@stud.pmu.ac.at (N.S.); an.schneider@salk.at (A.M.S.); k.moerwald@salk.at (K.M.); k.maruszczak@stud.pmu.ac.at (K.M.); j.gomahr@salk.at (J.G.)

³ Department of Paediatrics, Paracelsus Medical University, 5020 Salzburg, Austria

⁴ Department of Sport Medicine and Functional Explorations, Diet and Musculoskeletal Health Team, Human Nutrition Research Center (CRNH), INRA, University Teaching Hospital of Clermont-Ferrand, University of Clermont Auvergne, 63000 Clermont-Ferrand, France; vjulian@chu-clermontferrand.fr

⁵ Laboratory of Metabolic Adaptations to Exercise under Physiological and Pathological Conditions (AME2P), University of Clermont Auvergne, 63000 Clermont-Ferrand, France; david.thivel@uca.fr

⁶ Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, 8010 Graz, Austria; haral.mangge@medunigraz.at

* Correspondence: d.weghuber@salk.at; Tel.: +43-(0)-5-7255-57518



Citation: Pixner, T.; Stummer, N.; Schneider, A.M.; Lukas, A.; Gramlinger, K.; Julian, V.; Thivel, D.; Mörwald, K.; Maruszczak, K.; Mangge, H.; et al. The Role of Macronutrients in the Pathogenesis, Prevention and Treatment of Non-Alcoholic Fatty Liver Disease (NAFLD) in the Paediatric Population—A Review. *Life* **2022**, *12*, 839. <https://doi.org/10.3390/life12060839>

Academic Editors: Elvira Verduci and Giacomo Biasucci

Received: 29 March 2022

Accepted: 31 May 2022

Published: 5 June 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: Paediatric non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease in childhood. Obesity is the main risk factor. Nutrition and lifestyle are the key elements in preventing and treating NAFLD in the absence of approved drug therapy. Whilst recommendations and studies on macronutrients (carbohydrates, fat and protein) in adult NAFLD exist, the discussion of this topic in paediatric NAFLD remains contradictory. The purpose of this review is to provide state-of-the-art knowledge on the role of macronutrients in paediatric NAFLD regarding quality and quantity. PubMed was searched and original studies and review articles were included in this review. Fructose, sucrose, saturated fatty acids, trans-fatty acids and ω -6-fatty-acids are strongly associated with paediatric NAFLD. High consumption of fibre, diets with a low glycaemic index, mono-unsaturated-fatty-acids and ω -3-fatty-acids reduce the risk of childhood-onset NAFLD. Data regarding the role of dietary protein in NAFLD are contradictory. No single diet is superior in treating paediatric NAFLD, although the composition of macronutrients in the Mediterranean Diet appears beneficial. Moreover, the optimal proportions of total macronutrients in the diet of paediatric NAFLD patients are unknown. Maintaining a eucaloric diet and avoiding saturated fatty acids, simple sugars (mainly fructose) and a high-caloric Western Diet are supported by literature.

Keywords: paediatric; non-alcoholic fatty liver disease; NAFLD; macronutrients; obesity; carbohydrates; fat; protein; nutrition; diet

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the most prevalent type of chronic liver disease in the paediatric population. NAFLD affects 3–10% of the general paediatric population and up to 40–50% of children and adolescents with obesity or overweightness, and is expected to become the leading cause of liver failure in the Western world under the age of 18 years old [1–4]. Its prevalence in studies varies depending on the

diagnostic methods used, ethnicity, age, gender, geographical region and the population sampled [5]. NAFLD encompasses a disease spectrum ranging from hepatic steatosis (at least 5% of macro vesicular fat present in the liver) to non-alcoholic steatohepatitis (NASH) and hepatic fibrosis. It is traditionally defined by exclusion criteria, as morphological changes need to happen in the absence of significant alcohol consumption, genetic/metabolic disorders, infectious disease of the liver and steatogenic medications [6]. The diagnosis of NAFLD before the age of 3 years old requires reinvestigation for an underlying metabolic disease [7–9]. It must be noted that NAFLD is also diagnosed in normal-weight children (lean-NAFLD), with its prevalence ranging from 1.5–5% [3,10,11].

Obesity remains the most important risk factor for NAFLD [10,12], favouring metabolic impairments (e.g., insulin resistance, dyslipidaemia and impaired glucose tolerance) that affect the liver and cause NAFLD as early as childhood. Insulin resistance leads to increased gluconeogenesis and accumulation of hepatic fat. Hyperglycaemia promotes lipid accumulation in hepatocytes by stimulating lipogenesis [13,14], promoting the release of pro-inflammatory cytokines [15]. The process is bidirectional, as NAFLD in turn aggravates the inflammatory response in obesity [16,17]. NAFLD is considered the hepatic feature of obesity and metabolic syndrome [18,19]. Paediatric NAFLD is thus associated with an increased risk of disturbed glucose metabolism, arterial hypertension, renal dysfunction and chronic kidney disease, decreased bone mineral density, obstructive sleep apnoea (OSAS) and polycystic ovary syndrome (PCOS) [20–26]. In adults, NAFLD increases the risk of cardiovascular events eightfold, or threefold for type 2 diabetes, and it is a severe risk factor for hepatocellular carcinoma [27–29]. US children and adolescents first diagnosed with NAFLD frequently display features of NASH and advanced fibrosis has been present in 10–25% of these cases [30]. Children with NAFLD display a different histological pattern of the liver compared with adults, with evidence for a more aggressive disease phenotype [31–33]. Abdominal visceral obesity in particular correlates with histological damage and hepatic fibrosis in children [34].

NAFLD has been traditionally presented as a mere imbalance of too much caloric intake and insufficient physical activity. The over-consumption of food, especially that which is rich in total and saturated fats and refined sugar, is considered a major risk factor for the development of NAFLD and obesity. Children with NAFLD (biopsy-proven) have been reported to more likely consume a Western diet, but also to have a more sedentary lifestyle [35,36]. While normal-weight children have been shown to dedicate about 16 h per week to sedentary activities (e.g., reading, watching TV or playing video games and drawing), this time reaches about 25 h per week in children with NAFLD and overweight-ness [37,38].

In addition to behavioural factors, a number of genetic variants have been identified and associated with both paediatric and adult NAFLD. The variants in patatin-like phospholipase domain-containing-protein-3 (PNPLA3) are linked to progression to NASH and fibrosis. PNPLA3's gene expression is also directly related to the nutritional status. It is upregulated by over-nutrition and downregulated in a fasting state [39–43]. Mutations in the transmembrane-6 superfamily member 2 (TM6SF2) affect lipid secretion, variations in the glucokinase regulator (GCKR) affect monosaccharide uptake and lipid synthesis and MBOAT7 affects lipid metabolism. Other SNPs are known to affect mitochondrial functioning, transmembrane transport of sugars and bile acids and modify inflammatory pathways [16,44,45]. The influence of genetic variants on NAFLD is supported by prevalence variations among different ethnic groups, family clusters and the occurrence of lean NAFLD, as well as variable progression of liver disease in certain individuals with known variants [43,46].

Epigenetic factors (e.g., in utero development and maternal factors) are also considered as risk factors. They determine the risk of disease, not only in childhood, but also later in life [47]. Antenatal risk factors include hyperglycaemia in utero and gestational diabetes, maternal obesity and fructose intake, excessive weight gain during pregnancy, metabolic

syndrome during pregnancy, caesarean section, low and high birth weights, absence of breast feeding and early exposure to antibiotics [48–54].

Due to a lack of pharmacological options for the treatment of paediatric NAFLD, nutritional intervention and lifestyle modification remain recommended as a first-line treatment. The focus of nutritional intervention is on lowering energy intake and healthier eating profiles, while lifestyle aims at increasing physical activity (PA) and reducing sedentary behaviour [55,56]. The majority of studies on interventions in paediatric NAFLD focus on the combination of nutrition and lifestyle [57].

While there is a multitude of studies and recommendations for nutritional intervention in adult NAFLD, the optimal quantity and quality of macronutrients (carbohydrates, fat, protein) in paediatric NAFLD remains debated [58–62]. The current narrative review, therefore, aims to provide insight into what is known regarding the role of macronutrients in the development and nutritional therapy of paediatric NAFLD. It does not discuss nutritional supplements and vitamins, but solely macronutrients themselves and in the context of diets/dietary patterns.

2. Materials and Methods

We performed a literature search for this review using the electronic database PubMed. As this is a narrative review, no systematic criteria (e.g., PRISMA) were applied. The search parameters included original articles or reviews about patients (any sex, age, race or comorbidity were included). The first search without filters was performed using the terms “NAFLD” and “carbohydrates” and “fat” and “protein” for publications until 31 December 2021. In an additional search, the parameters “NAFLD” and “macronutrients” (articles up to and including 31 December 2021) were searched for. Emphasis was put on the paediatric population. For the purpose of this review, the paediatric population was defined as being under the age of 18 years old. Secondary literature (references from studies and reviews) was also reviewed.

3. Results

3.1. General Findings

The first literature search resulted in 1049 articles and the second search resulted in 754 publications. Two of the authors (TP and DF) reviewed the articles. After screening the titles and abstracts, a total of 361 articles of relevance remained. Of these, 283 were used to write this narrative review.

At present, there is no specific diet that is universally recommended for nutritional therapy in paediatric patients with NAFLD. Overall, most studies and societal guidelines give general recommendations, mentioning a low-caloric healthy diet (low in carbohydrates, fructose, saturated fatty acids and trans-fatty acids, but prioritising low-glycaemic-index foods) [63,64]. With regards to lifestyle interventions and weight reduction, no systematic difference is made between children and adolescents with obesity and/or NAFLD [65,66].

The American Heart Association suggests a balanced diet consisting of vegetables, fruits, low saturated fats, whole grain and fish, with low fructose and salt intake [67,68]. While some authors state that no diet is clearly superior, some advocate for the Mediterranean Diet [57,69–73]. Avoiding the overconsumption of the previously mentioned macronutrients and therefore the resulting obesity is a key point in preventing and treating NAFLD [74]. No author or guideline mentioned a concrete caloric restriction, specific meal composition, meal frequencies and distribution of macronutrients (e.g., protein in the evening and carbohydrates in the morning) or a specific recommendation that differed from general healthy diet recommendations. Dietary recommendations are generally observation based and there has been only a small number of randomised controlled trials of diet as a monotherapeutic approach for paediatric NAFLD [57,68,75].

As most patients with NAFLD suffer from obesity or overweightness, caloric restriction is a consistent recommendation for the treatment of adults and children with NAFLD. However, some controversy remains regarding the role of caloric restriction in treating

paediatric NAFLD [76]. Mouzaki et al. argue that it is difficult to clarify the role of a specific macronutrient vs. the total caloric intake [69]. Eslamparast et al. state that caloric restriction is the most important element in the dietary treatment of NAFLD. Special emphasis is put on the avoidance of high amounts of carbohydrates, simple sugars, fat and protein, as well as low fibre intake [74].

A general point of agreement is that the quality of the macronutrient is essential, as is an individualised approach to therapy. A poor-quality diet (e.g., convenience foods and those high in saturated fat and sugars) may even cause NAFLD in the absence of obesity [74,75,77,78]. Panera argues that the composition of macro- and micronutrients is more important in the pathogenesis and treatment of NAFLD than the total energy intake [43]. Another point of agreement is that nutritional intervention should be paired with physical exercise and the reduction of sedentary behaviour [57,67]. Recent studies suggest that a reduction in the intake of simple carbohydrates (especially high fructose/sucrose) and saturated fats benefits the prevention of paediatric NAFLD [46,63,74]. There is evidence for a metabolic threshold. This describes a relative body fat content that needs to be achieved before high amounts of fructose and other high-caloric macronutrients lead to hepatic and metabolic impairment [79]. The consumption of food enriched in fat and fructose may alter the gut microbiome and the intestinal barrier function, thus leading to endotoxemia and low-grade inflammatory processes [43,80,81].

3.2. *Macronutrients*

Although general recommendations for macronutrients exist (see above), the influence of macronutrient intake and composition in paediatric NAFLD remains a topic of major interest.

Vos et al. stated that there was no significant difference between the fraction of calories consumed from fat, carbohydrates and protein in children with steatosis and NASH [82]. Anderson et al. reported inconsistent associations between absolute macronutrient intake and liver outcomes. They found evidence neither for a particular macronutrient, nor that intake at a particular age was strongly associated with hepatic outcomes [83]. Similarly, Gibson et al. found no significant differences in macro- and micronutrient intake between biopsy-proven paediatric NAFLD and obese controls. Therefore, they recommended that paediatric NAFLD patients should follow general paediatric recommendations for weight loss and not specific guidelines [84]. These three studies contradict general findings focusing on fat and carbohydrate reduction (especially fructose) as primary targets in nutritional intervention. In the following paragraphs, each macronutrient is reviewed on its own.

3.2.1. Carbohydrates

Carbohydrates—General Recommendations

The World Health Organization (WHO) currently recommends a reduction of free sugar (primarily sucrose and fructose) intake to less than 10% daily of the total energy intake (see Table 1 for WHO recommendations) [85]. In general, the majority of calories consumed are provided by carbohydrates. The intake of total energy and carbohydrates are higher in children and adolescents with NAFLD than in healthy children [86]. Carbohydrates can be grouped into sugars—monosaccharides, disaccharides, oligosaccharides and polysaccharides—and sugar alcohols. While several carbohydrates have been associated with NAFLD, the primary focus is on fructose [69,87]. In addition, added sugar that stems from glucose and fructose is pivotal to NAFLD development [86]. For example, in US adolescents, average consumption of 94 g of added sugar daily, equalling 17.9% of energy intake, has been reported [53,54,88–90].

Table 1. WHO macronutrient recommendations in all children.

General WHO Recommendations for Macronutrients in Children [91–94]	
Carbohydrates	<10% daily of total energy intake
	Reduction of free sugar intake (primarily sucrose and fructose)
Fat	≤30% of total energy intake
	Saturated fats intake: <10% of total energy intake
	Trans fats intake: <1% of total energy intake
Protein	Male (3–18 years old): 0.9 g/kg/day
	Female (3–15 years old): 0.9 g/kg/day
	Female (15–18 years old): 0.8 g/kg/day

Carbohydrates in the Pathogenesis of Paediatric NAFLD

A diet rich in carbohydrates provides the major source for hepatic free-fatty-acid (FFAs) synthesis. In children with NAFLD, the production of FFAs from carbohydrates contributes 30% of the total FFAs, whereas in healthy children, high carbohydrate intake produces only 5% of total FFAs [95]. The effect of carbohydrate conversion to triglycerides and development of NAFLD has been more closely associated with fructose and sucrose than with glucose [96].

Additional glucose promotes lipid synthesis via the activation of the transcription factor carbohydrate-responsive element-binding protein (ChREBP). Dietary glucose and fructose have different effects on mitochondrial protein acetylation and malonyl-CoA. This results in a greater reduction in fatty acid (FA) oxidation and greater lipid synthesis in response to the extra-fructose diet compared with the extra-glucose diet [97–99].

Carbohydrates in Treatment and Prevention of Paediatric NAFLD

Low-carbohydrate diets may improve weight loss and reduce hepatic steatosis, as well as reduce triglycerides (TGs) and increase the HDL levels [100–103]. In a 2019 study, Schwimmer et al. investigated 11–16-year-old boys with NAFLD ($\geq 10\%$ liver fat content). The boys were assigned to either a low-sugar diet or a regular control diet. The study aimed to provide less than 3% of their daily energy from added sugars (intervention). During the study, the low-sugar diet reduced the liver fat content by 8% (compared with 1% in the control diet group). No significant changes in TGs or fasting insulin were noted, but there was an improvement in plasmatic liver enzymes [104]. In a 2020 study, Goss et al. reduced the liver fat content by 6% via a carbohydrate-reduced diet over the course of 8 weeks. In this study, girls and boys with obesity and NAFLD were assigned to either a low-carbohydrate or a low-fat diet. The low-fat diet resulted in a reduction in liver fat of 1%. The study demonstrated carbohydrate restriction as being superior to a low-fat diet when the daily caloric requirement was maintained, not only resulting in a reduction in the hepatic fat content, but also an improvement in insulin resistance [76].

Both studies provide evidence that a general reduction in carbohydrates can result in a reduction in the hepatic fat content and improvement in metabolic parameters.

Fructose and Sucrose—Fructose and Sucrose in the Epidemiology and Pathogenesis of Paediatric NAFLD

The consumption of fructose has increased over the past several hundred years and dramatically over the past few decades in parallel with the consumption of sucrose and high-fructose corn syrup (HFCS) [91]. Since the 1980s, an increase as high as 300% over a period of 20 years has been recorded. Studies claim that fructose may be as addictive as certain drugs [87,105,106]. The consumption of fructose and sucrose has equalled the epidemic rise in paediatric obesity and NAFLD [69,91,107–113].

In its natural form, fructose and sucrose can be found in fruits, vegetables and a great number of foods and beverages. Fructose, sucrose and HFCS can also be found in large quantities in processed foods and sugar-sweetened beverages. This is especially relevant as children and adolescents with NAFLD consume significantly more soft drinks than the general population [114]. NAFLD patients generally consume nearly two to three times more fructose (365 kcal) than healthy controls (170 kcal) [38]. It is relevant that the majority of fructose does not come from fruits or vegetables in paediatric NAFLD patients, but from processed foods. In a collective of 8–16-year-olds, only 25% of NAFLD patients consumed one or more fruits per day. In normal-weight children, daily fruit consumption was the case in 64.7%, and in 45% of children with obesity but without NAFLD. In contrast, an epidemiological study from Finland found an inverse relationship between fructose intake and NAFLD. However, in this study, the majority of fructose was consumed through fruit intake. Fruits contain less fructose than soft drinks and processed foods, but also contain constituents (flavanols, epicatechin, ascorbate and other antioxidants) that may antagonise the negative metabolic and inflammatory effects of fructose [115,116].

In 2014, Sullivan et al. demonstrated that the absorption and metabolisation of fructose is more effective in children with NAFLD than in lean, healthy children, and also resulted in an exacerbated metabolic profile [117]. Fructose and sucrose were found to interact with transcriptional factors affecting the gene expression involved in glycolysis and lipogenesis [118].

Studies have demonstrated that fructose is associated with increased insulin resistance, leptin resistance and a decrease in adiponectin (the latter two being hormones produced by adipocytes) [69,110,111]. Leptin resistance is induced by chronic fructose consumption. Even before weight gain, it aggravates high-fat-induced obesity. This effect is fully reversible when fructose is eliminated from the diet. Leptin is an anorexigenic hormone; hence, in leptin resistance, satiety cannot be achieved [110,111]. Adiponectin is decreased in patients with obesity and involved in lipid and carbohydrate metabolism. High-fructose diets also reduce the activity of PPAR α and hepatic lipid oxidation, and stimulate NF- κ B expression. In animal studies, this has led to oxidative stress, as well as hepatic steatosis and hepatic fibrosis. Fructose is absorbed in the small intestine via the GLUT5 transporter and is taken up by the liver, testes and other organs. (Over)consumption of a fructose-rich diet induces de novo lipogenesis, causing elevated triglyceride and cholesterol levels with dyslipidaemia [119].

Whether fructose consumption induces gut leakiness and intestinal dysbiosis remains under discussion [120]. Sullivan et al. suggested altered intestinal bacterial flora fermentation (fructose into hydrogen) or an up-regulation of the GLUT5 transporter in the intestinal epithelium to be at the root of dysbiosis [117]. Jones et al. reported that a high-fructose diet was associated with lower abundance of beneficial microbes (*Eubacterium* and *Streptococcus*), which are involved in carbohydrate metabolism, aiding dysbiosis [121]. A 2020 study by Aleman et al. demonstrated that a daily dose of 75 g of fructose in obese patients did not cause increased gut permeability or endotoxemia [122]. This contradicts previous reports that stated that fructose causes bacterial overgrowth, an increase in intestinal permeability, precipitating endotoxemia and, hence, the initiation of an inflammatory cascade driving the progression of NAFLD [123,124].

It has been reported that regular consumption of fructose or sucrose in a caloric-stable diet increases the synthesis of fatty acid synthesis, an effect that is not present with glucose [125]. Studies on isocaloric diets using sucrose (glucose–fructose disaccharide) or a 50:50 mixture of glucose and fructose showed that the mixture of monosaccharides induced slightly more steatosis of the liver [126]. Studies have also shown the additive effect of a diet high in fat and sucrose on the development of NAFLD [127].

Fructose and Sucrose—Fructose and Sucrose in the Treatment and Prevention of Paediatric NAFLD

In nutritional studies, it has been shown that lowering fructose, sucrose and HFCS intake may be protective against the development of NAFLD in children with obesity. As sucrose is 50% fructose and 50% glucose, it must be considered that a reduced intake of sucrose also results in a reduced intake of fructose. Studies cited in this review specifically listed fructose or sucrose. The amount of fructose was shown to be more relevant than the total amount of carbohydrates in general, and the amount of fructose consumed at the age of 14 years old was a predictor of the presence of NAFLD at the age of 17 years [128]. Studies reported that it normally takes at least 8–24 weeks of a high fructose-diet to develop NAFLD [129]. Fructose-induced NAFLD is also able to develop in the absence of weight gain [130]. Even short-term interventions of nine days of isocaloric fructose restriction could show decreases in liver fat, visceral adipose tissue and de-novo lipogenesis, as well as improved insulin profiles [131]. The FRAGILE study was able to demonstrate that a decrease in fructose intake reduces markers of liver dysfunction in children and adolescents with NAFLD [79]. In a study by Jin et al. during a 4-week randomised controlled double-blinded beverage intervention study, it was reported that reduction in dietary fructose in Hispanic American adolescents with NAFLD improved several plasma markers associated with metabolic syndrome (e.g., adipose insulin sensitivity, high-sensitivity C-reactive protein and low-density lipoprotein oxidation) [132].

In healthy subjects, trials of a 4-week moderate (1.5 g/kg/day) and 7-day high-fructose (3.5 g/kg/day) supplementation demonstrated the negative effects of additional fructose. In the 7-day trial, dyslipidaemia and ectopic lipid deposition in the liver and muscles occurred, while the moderate 4-week modification led to an increase in the plasmatic TG and glucose levels [133,134]. This is in accordance with adult data, showing that even shorter periods (6 days) are sufficient to induce dyslipidaemia, as well as hepatic and adipose tissue insulin resistance in healthy subjects with a high-fructose diet (3 g/kg/day) [135].

Despite these findings, fructose is not universally believed to cause NAFLD on its own. It is, however, thought that fructose may favour NAFLD progression on the basis of pre-existing risk factors (e.g., obesity, metabolic syndrome or diabetes) [136,137]. Silbernagel et al. added 150 g/d of fructose or glucose to an otherwise balanced, weight-maintaining diet for 4 weeks in a collective of adolescents. No changes in the amount of hepatic, visceral and subcutaneous fat were found [138].

Fructose is rarely consumed alone, and the effects of fat and fructose have been demonstrated to be additive in the progression of NAFLD. A dietary combination of high fat and fructose resulted in a higher risk of NAFLD and liver fibrosis in adult and rodent studies [128,139].

Sugar-Sweetened Beverages and Energy Drinks

Sugar-sweetened beverages or soft drinks (soda, soda pop, cola and tonic) are beverages with a generous amount of high-fructose (corn syrup) or an equally high amount of sucrose [140–142]. Over the previous few decades, paediatric consumption of sugar-sweetened beverages, energy drinks and alcohol has increased dramatically [143]. In a study conducted by the European Food Safety Authority (EFSA), 68% of adolescents and 18% of children consumed sugary (energy) drinks on a regular basis [144]. The consumption of soft drinks is associated with paediatric NAFLD and the severity of hepatic fibrosis in a dose-dependent manner [38,87,92,137,145,146].

In adults, consuming more than one soft drink per day (360 mL) was associated with increased risk of the development of metabolic syndrome [147,148]. Table 2 provides a summary of the results for carbohydrates and paediatric NAFLD.

Table 2. Summary of the results for carbohydrates and paediatric NAFLD (abbreviations: CHO (carbohydrates), NAFLD (non-alcoholic fatty liver disease), malonyl-CoA (malonyl-Coenzyme-activator)).

Summary Table for Carbohydrates and Paediatric NAFLD	
Pathogenesis:	Overconsumption of CHO as a risk factor [95]
	More free fatty acids are synthesised from CHO in paediatric NAFLD [95]
	Additional glucose promotes lipid synthesis [97–99]
	Additional glucose impairs mitochondrial protein acetylation and malonyl-CoA [97–99]
	Fructose/sucrose: affect gene expression involved in glycolysis and lipogenesis [118]
	Fructose: associated with increased insulin resistance and leptin resistance, and a decrease in adiponectin [69,110,111]
Treatment and prevention:	Low glycemic index diet benefits BMI [149–151]
	Avoid sugar-sweetened beverages [38,87,92,137,145,146]
	Low-CHO diets may improve weight loss and hepatic steatosis (minus 6–8% in liver fat), insulin resistance, triglyceride and HDL levels
	Avoid processed glucose/fructose [36]
	Fructose: lowering intake may be protective against of NAFLD in children with obesity [131]

3.2.2. Fat

Fat—General Recommendations

The WHO recommends that the total fat intake should not exceed 30% of the total energy intake. The intake of saturated fats should be less than 10% and trans-fat intake should be less than 1% of the total energy intake (see Table 1 for WHO recommendations). Furthermore, a shift in the fat consumption away from saturated fats and trans-fats to unsaturated fats is recommended, with the aim of eliminating industrially produced trans-fats [152]. The American Heart Association (AHA) advises to keep the daily fat intake between 30 and 35 percent of calories for children 2 to 3 years of age and between 25 and 35 percent of calories for children and adolescents 4 to 18 years of age. Most fats should come from sources of polyunsaturated and monounsaturated fatty acids, such as fish, nuts and vegetable oils [153].

Fat in the Pathogenesis of Paediatric NAFLD

Consumed fat is mainly TGs that are processed in the intestine and resorbed by enterocytes. Cholesterol is only resorbed at a small percentage from animal products (e.g., eggs and meat). Fatty acids (FA) then reach the liver, where they can either be esterified or oxidated and accumulated or secreted. FA can be differentiated into saturated FA (SFA), monounsaturated (MUFAs) or polyunsaturated fatty acids (PUFAs) [154,155].

There is an association between fat intake and increased risk of NAFLD. As with carbohydrates, it is more dependent on the type of fat than the total amount consumed [46,156,157]. As previously mentioned, fat and carbohydrates (especially fructose) exert an additive effect when causing NAFLD in the paediatric population [128,139]. A fat-rich diet has been found to induce hepatic steatosis and visceral adiposity [158,159]. Fat-reduced isocaloric diets have also been able to reduce the liver fat content [160].

The quality of fat is not only essential in nutrients, but also on a plasmatic level. Mitchel et al. reported that reducing free fatty acids in the blood flow towards the liver improves steatosis, insulin sensitivity and ALT [75]. In this context, hepatic lipotoxicity is

not solely caused by triglyceride accumulation per se, but induced by free fatty acids, free cholesterol and different lipid metabolites (e.g., lysophosphatidylcholine) [161,162].

Fat in the Treatment and Prevention of Paediatric NAFLD

Exchanging saturated fatty acids with polyunsaturated (PUFAs) or monounsaturated fatty acids (MUFAs), as advised by the WHO, within isocaloric diets has been shown to improve hepatic fat accumulation [163,164]. Nutritional MUFAs can be found in natural foods, such as milk products, nuts, olive oil, red meat and high-fat fruits, such as olives and avocados [165]. Sunflower oil contains as much as 85% MUFA, and olive oil contains 75% MUFAs. MUFAs reduce the LDL cholesterol, oxidised LDL, TC and TGs levels without decreasing HDL. Replacing carbohydrates and saturated fats with MUFAs reduces glucose and blood pressure and increases HDL in diabetic subjects [165–169]. Nutritional PUFAs can be found in walnuts, sunflower seeds, sesame seeds, peanut butter and peanuts, flaxseed, poppy seeds, avocado oil, olive oil and safflower. The types of PUFA are omega-3 (ω -3) and omega-6 (ω -6) fatty acids. Examples of ω -3 fatty acids are docosahexaenoic acid (DHA), linolenic acid (plant oil) and eicosapentaenoic acid (EPA) (fish oil). Sources of ω -6 fatty acids include eggs, whole-grain foods, walnuts, pumpkin seeds and pine nuts [170]. ω -3 fatty acids are beneficial; however, ω -6 fatty acids should be avoided due to their ability to increase inflammatory processes [171]. Ω -3 fatty acids are ligands of PPAR- α . Low levels of ω -3 PUFAs impair hepatic PPAR- α activity. This decreases mitochondrial lipid β -oxidation and upregulates lipogenic transcription factors (e.g., sterol regulatory element-binding protein 1c) [93,172].

In adult NASH patients, not only a high intake of ω -6 fatty acids, but also an abnormal ω -3/ ω -6 ratio has been reported [173]. The recommended ω -3/ ω -6 ratio is 1:1 to 1:4. A reduction of SFAs in the daily diet and sufficient consumption of ω -3 fatty acids to improve NAFLD in children is advised [70,174,175]. Contrastingly, ω -3 fatty acid supplementation over the course of 6 months in NAFLD children did not improve the ALT levels [132,176,177], while, in another study, the supplementation of ω -3 fatty acids in children with NAFLD over a period of 18 months improved the ALT levels significantly [70].

Diets poor in PUFAs have shown clear association with the development of paediatric NAFLD [178,179]. The increased consumption of saturated long-chain fatty acids (SLCFAs, e.g., palmitic acid, myristic acid and stearic acid), particularly in animal products, causes mitochondrial dysfunction, increased oxidative stress as well as low-grade inflammation [180].

SLCFAs also increase insulin resistance (IR), and the avoidance of SLCFAs benefits IR [181,182].

Furthermore, Anderson et al. stated that the results on fat and paediatric NAFLD remain controversial. Saturated fatty acids (SFAs) have been reported to increase steatosis of the liver proportionally to consumption, as have a high percentage of saturated and a low percentage of polyunsaturated fat consumption in paediatric NAFLD. In a different study, the association between saturated fat intake and NAFLD was reported to be inverse, while in another collective, no association between saturated fat intake and NAFLD could be made [82,83,183–185]. Table 3 provides a summary of the results for fat and paediatric NAFLD.

3.2.3. Protein

Protein—General Recommendation

The WHO and Food and Agriculture Organization (FAO) recommend a protein intake of 0.9 g/kg/day from 3 to 18 years of age for boys and from 3 to 15 years of age for girls. Between 15 and 18 years of age, the amount decreases slightly for girls to 0.8 g/kg/day (see Table 1 for WHO recommendations) [92].

Table 3. Summary of the results for fat and paediatric NAFLD (abbreviations: CHO (carbohydrates), NAFLD (non-alcoholic fatty liver disease), MUFAs (mono-unsaturated fatty acids), PUFAs (poly-unsaturated fatty acids), LDL (low-density lipoprotein), TC (total cholesterol), TGs (triglycerides), HDL (high-density lipoprotein), PPAR- α (peroxisome proliferator-activated receptor alpha).

Summary Table for Fat and Paediatric NAFLD	
Pathogenesis:	
	Overconsumption of fat as risk factor [15,46,156]
	Fat and CHO have additive effects in causing NAFLD [128,139]
	Hepatic lipotoxicity, mitochondrial dysfunction, impairment of beta-oxidation and increased oxidative stress, as well as low-grade inflammation [16,17]
	MUFAs reduce LDL cholesterol, oxidised LDL, TC and TGs levels without decreasing HDL [165–169]
	Low levels of ω -3 PUFAs impair hepatic PPAR- α activity [93,172]
Treatment and prevention:	
	Exchanging saturated fatty acids with polyunsaturated (PUFAs) or monounsaturated fatty acids (MUFAs) in isocaloric diets [163,164]
	MUFAs: in milk products, nuts, olive oil, red meat and high-fat fruits, such as olives and avocados [165]
	PUFAs: in walnuts, sunflower seeds, sesame seeds, peanut butter and peanuts, flaxseed, poppy seeds, avocado oil, olive oil and safflower [170]
	ω -3 PUFAs recommended [70,174,175]
	Recommended ω -3/ ω -6 ratio is 1:1 to 1:4. [70,174,175]

Protein in the Pathogenesis of Paediatric NAFLD

Protein is the least-studied macronutrient concerning pathophysiology and nutritional intervention in paediatric NAFLD [46,186]. From a physiological point of view, protein intake is important for hepatocyte regeneration; it also provides important amino acids for preventing hepatic fat deposition [187].

A number of studies have reported a significantly higher protein intake in patients with NAFLD than in healthy individuals [188–191], while others found no difference [77,192]. Elevated protein intake may have both beneficial and harmful effects on NAFLD. Some authors report that high protein intake reduces the hepatic fat content [193,194]; other authors, however, suggest that it may increase hepatic fatty acid oxidation and the secretion of fatty acids from the liver [156]. High protein intake may be harmful by influencing gut microbiota fermentation, as it may lead to SCFAs and other intestinal metabolites (e.g., phenols, branched-chain fatty acids and ammonia), thus possibly harming the intestinal barrier's integrity [195]. A moderate-protein diet (25% of total energy intake) was reported to be without side effects and to reduce the body fat content, similar to a high-protein diet. Hence, authors have proposed a moderate protein diet for NAFLD patients [196].

However, other studies report that malnutrition and protein deficiency also induce hepatic steatosis and NASH [187,197], and are associated with excessive triglyceride storage and NAFLD [198]. A low-protein diet by itself may lead to IR, high blood pressure and lipid abnormalities. These mechanisms are also involved in the development of NAFLD [100,199,200].

Protein in the Treatment and Prevention of Paediatric NAFLD

Special diets that are high in protein and low in carbohydrate improve insulin homeostasis, the lipid profile and liver enzymes. Soy protein has been shown to reduce the

plasma cholesterol levels and fat deposition in NASH [201]. Table 4 provides a summary of the results for protein and paediatric NAFLD.

Table 4. Summary of the results for carbohydrates in Table 3. Summary table for protein and paediatric NAFLD (abbreviations: IR (insulin-resistance), NAFLD (non-alcoholic fatty liver disease)).

Summary Table for Protein and Paediatric NAFLD	
Pathogenesis:	
	Protein intake is important for hepatocyte regeneration [187]
	Protein provides important amino acids for preventing hepatic fat deposition [187]
	Elevated protein intake may have both beneficial and harmful effects on NAFLD [193,194]
	Low-protein diet by itself may lead to IR, high blood pressure and lipid abnormalities [100,199,200]
Treatment and prevention:	
	Moderate-protein diet (25% of total energy intake) was reported to be without side effects and recommended for NAFLD patients [196]
	Results inconclusive [188–191,193,194]

3.3. Special Issues

3.3.1. Diets

While macronutrients are of great interest, studies tend to compare diets. Results on what the ideal dietary intervention for paediatric NAFLD is remain controversial and, in meta-analysis, no diet has been identified to be superior so far [68]. Long-term compliance with diets is poor and reduced adherence has been associated with a greater increase in liver enzymes [202]. Thus, the management of NAFLD requires multidisciplinary management, including dietitians, psychologists and clinical nurse specialists, to achieve the best results and adherence [203].

Low-Caloric Diet

The avoidance of overconsumption and reduction of SFA and free sugar are generally agreed upon components for NAFLD treatment [63,64]. The question of isocaloric vs. hypocaloric diet, however, is complex. Weight loss is considered a main factor beneficial to NAFLD, as obesity and overweightness are common. In meta-analysis, it has been shown that greater weight loss benefitted the improvement of non-invasive NAFLD-markers [68,203]. Weight reduction of 7% to 20% leads to significant improvement in paediatric NAFLD [94,204–207]. Rapid weight loss is not recommended due to the risk of increasing hepatic inflammation [63].

In a low-calorie diet study combined with weekly nutritional counselling and aerobic exercise (30–45 min/day at least three times per week) by Nobili et al., which was performed for the duration of a year, a significant reduction in BMI resulted in improvements in fasting glucose, insulin levels, serum lipid levels and aminotransferases and hepatic steatosis in sonography. The diet featured 25–30 calories/kg/day, and the constitution of macronutrients was 50–60% carbohydrates, 23–30% fat and 15–20% protein. It also included saturated and unsaturated fatty acids (FA), as well as a 4:1 omega-6/omega-3 ratio [94].

These results were confirmed in a longitudinal randomised controlled trial regarding lifestyle. In a Danish study, 117 children with obesity took part in a 10-week ‘weight loss camp’. After the ten weeks, a year of subsequent dietary and exercise interventions followed. The average weight loss was about 7 kg. Only 71 children completed the trial and showed improvement concerning insulin sensitivity, serum aminotransferases and hepatic

steatosis. Over the 12-month follow-up period, only 25% of participants maintained the weight reduction [208].

It has been reported that, as long as weight loss is achieved, a hypocaloric diet, either based on low carbohydrates or low fat, results in comparable reductions in intrahepatic fat [176,209].

Mann et al. reported that the most commonly used hypocaloric diets with low fat contain 25–30 kcal/kg, 50–60% carbohydrates and 23–30% fat (with one-third saturated fat) for nutritional intervention in paediatric NAFLD studies [68,202,203,210,211].

Low-Carbohydrate Diets/Low-Glycaemic-Index (GI) Diets

In the FRAGILE study, a specific diet (low fructose/low glycaemic index/low glycaemic load) was investigated in children and adolescents with NAFLD, as well as in healthy individuals. The glycaemic index (GI) is used as a measure of the availability of carbohydrate or the ability of an ingested nutrient to elevate blood glucose. For this purpose, foods are classified as low, medium, or high GI. A GI under 55 is considered low, while 70 and above is considered high GI. Glucose (GI = 100) is high, while sucrose (GI = 65) is considered medium and fructose (GI = 19) is considered low [212–214].

It was demonstrated that the absolute fructose intake was strongly associated with plasma aminotransferase, systolic blood pressure, body fat, insulin resistance and serum cholesterol, independent of weight loss [79].

As previously noted, fructose (like sucrose) appears to be a co-factor, but not sole cause, of paediatric NAFLD. As mentioned, evidence supports the fact that there is a significant difference between low-carbohydrate and low-fat diets, as long as both are calorie-restricted diets [215].

Diets low in carbohydrates may be helpful to achieve weight reduction if consumed for a short period (six months). However, weight loss can hardly be maintained after a year by continuing the diet [100].

In order to achieve long-term improvement of hepatic steatosis and improvements in IR, a moderately carbohydrate-restricted diet (CRD) may prove sufficient [76].

This CRD, as presented by Goss et al. for adolescents, aims at minimising the intake of refined carbohydrate sources (e.g., added sugars, high-glycaemic grains and fructose) and to provide $\leq 25\%$ energy from carbohydrates, 25% energy from protein and $\geq 50\%$ energy from fat. The intake of saturated fat was limited to $<10\%$ total energy/day. They reported that, when compared to a fat-reduced diet, the CRD resulted in significant reductions in weight, BMI, BMI z score, total fat mass and abdominal and leg fat. After the consumption of the CRD, a 32% decrease in the hepatic fat fraction from the average baseline value was achieved. Gross et al. concluded that the dietary recommendation of calorie restriction for weight loss may not be optimal for the reversal of fatty liver in a paediatric population. They concluded that their data suggest that energy restriction may be unnecessary in effectively treating paediatric NAFLD, and significant reductions in the hepatic fat fraction in adolescents can occur in a relatively short period of time (8 weeks) by consuming a CRD [76].

Results are conclusive for low-caloric and low-carbohydrate diets, but are contradictory for isocaloric diets with altered carbohydrate contents and paediatric NAFLD patients. In a collective of 102 children (aged 7–12 years), a low-carbohydrate, high-fat diet was comparable to the control group consuming a standard meal portion [149]. The majority of studies obtained through the literature search focused on carbohydrate reduction in the paediatric population, and only a limited number were found on low-glycaemic index-diets. These diets focused on weight reduction in obesity, but not specifically NAFLD-treatment. Studies comparing low-glycaemic-index diets to a reduced-fat diet in adolescents have shown better improvement of BMI among the low-glycaemic-index groups [149–151].

Low-Fat Diet

General recommendations concerning nutritional fat have already been discussed (e.g., avoiding SFA and consumption of ω -3 PUFAs). The most frequently used hypocaloric diets are of a low-fat content (25–30 kcal/kg and 23–30% fat (with one-third saturated fat)) for nutritional intervention in paediatric NAFLD-studies [68,202,203,210,211].

When compared with carbohydrate restriction, fat restriction was inferior for the improvement of paediatric NAFLD [76].

Mediterranean Diet

The Mediterranean diet (MD) is a diet that has its origins in the states surrounding the Mediterranean Sea. There is no single MD, as all countries have their own variations [216]. The MD consists primarily of vegetables and fresh fruit, olive oil, unrefined cereals and nuts. Fish, white meat and legumes are consumed in moderation. Red meat, processed meats and sweets are rarely consumed. The profile of fatty acids is considered beneficial as there is limited intake of saturated fat and cholesterol and high intake of MUFAs, as well as a balanced ω -3/ ω -6 ratio [217–220].

Due to the beneficial lipid profile, the high content of antioxidants and fibre and low content of simple sugars, the MD is assumed to be anti-inflammatory [163,164,221–223].

Therefore, the MD is considered a healthy and simple dietary regimen that is supported by a number of authors to prevent or treat paediatric NAFLD [70–73,224].

Western Diet

The Western diet is hypercaloric and high in fats and simple sugars. This diet is defined by high consumption of fast food, red meat, processed meats, full-fat dairy products, fried potatoes, refined cereals, cakes, biscuits, sweets, soft drinks, sauces and dressings [35]. As a consequence, the postprandial plasma glucose and insulin levels are quickly rising. The western diet is associated with increased hepatic de novo-lipogenesis, hepatic steatosis, insulin resistance, obesity and NAFLD [35,139].

This dietary pattern, if present at the age of 14 years, was shown to be associated with a higher prevalence of NAFLD at the age 17 (independent of sex, frequency of physical activity and sedentary behaviour and family income) [35,207].

Ketogenic Diet

In recent years, the ketogenic diet has become more popular. It has been reported that it leads to significant weight loss and reduces the hepatic fat fraction, as well as improves metabolic parameters in patients with obesity. A ketogenic diet is low in carbohydrates and, while being high in fat and/or protein, it is hypocaloric. It is not recommended for children with NAFLD. Maintaining a ketogenic diet over a longer period may aggravate NAFLD and the progression of systemic glucose intolerance, as demonstrated in animal studies [100,221,225].

Red Meat

The intake of meat has been associated with glucose intolerance and impaired insulin sensitivity, and may increase the risk of T2D in adults. The metabolic features are also present in NAFLD [226,227]. Grilled meat, predominantly red meat, was found to be associated with NAFLD [228]. In a study by Shi et al., the consumption of red meat was significantly associated with the prevalence of NAFLD, while this was not the case for white meat consumption [229,230].

3.3.2. Dietary Patterns

Dietary patterns concerning frequency, unusual mealtimes and amount of nutrients, as well as the selection of diet are crucial. The quality of food (processed foods and low intake of fruit and vegetables) impacts health and the progress of obesity and NAFLD [231–234]. It is known that fast eating, irregular meals with multiple feedings and consuming meals

on one's own are potentially harmful in developing eating disorders, obesity and, as a potential consequence, NAFLD. The parents' function as a positive role model has been discussed [235–241].

4. Discussion

Dietary recommendations for paediatric NAFLD primarily focus on weight loss and support the same regimen as that for treating paediatric obesity [46,242]. General nutritional recommendations focus on a low-caloric healthy diet (low in carbohydrates, fructose, sucrose, HFCS, saturated fatty acids and trans-fatty acids). Currently, there is no specific recommendation for the type of diet and amount of calorie restriction [64]. Low-caloric diets are investigated in studies as either low in carbohydrate and/or low in fat. The results claimed no difference between low fat and low carbohydrate, as long as it was low caloric [176,209]. As obesity is the main risk factor for NAFLD, caloric restriction is associated with weight reduction, thereby benefitting NAFLD (via ALT, ultrasound, MRI and liver biopsy) [10]. Not all authors advocate caloric restriction, but mention the importance of high-quality macronutrients. It is difficult to distinguish the specific effect of the macronutrient per se vs. overall caloric restriction in achieving weight loss. While (iso)caloric restriction appears sensible, hypocaloric diets do not [243]. In striving for weight loss, neglecting macronutrients and needed energy may cause health impairments. This may lead to the disturbance of development, puberty, bone density and potentially worsened NAFLD. It has been reported that prolonged hypocaloric diets (e.g., a ketogenic diet) or rapid weight loss may cause further liver damage [63]. This is also the case with low-carbohydrate diets, as they lead to swift weight loss and improvement of NAFLD over a short period but, if maintained for more than a year, may cause further liver damage [208].

In adults, weight loss of 3–5% can reduce hepatic steatosis and benefit metabolic parameters. NASH can be improved or resolved when more than 7% weight loss is achieved [244,245]. In paediatric NAFLD, the percentage of weight loss necessary to improve NAFLD has been described to be between 7% and 20% [94,204–207]. Weight reduction should be gradual and not exceed 500 g/week [75]. Moreover, long-term lifestyle changes lead to improved liver histology [246]. Nobili et al. reported that weight loss of >20% over a period of 12 months resulted in improved serum ALT and steatosis in ultrasound. The study did not give any details on the diet used, but provided caloric restriction and exercise advice [207,247]. In a different paediatric study, a mean weight loss of 5 kg (over a 24-month period) resulted in improvements in steatosis, lobular inflammation and liver enzymes [203]. There is no information about the point at which weight loss can be stopped to achieve and maintain hepatic health, or if all patients must aim for normal weight. An important part is that weight loss is not an option for lean patients with NAFLD [94,204–207].

The Western diet is the diet predominantly associated with NAFLD. It is characterised by the overconsumption of simple sugars and fats. Increased energy intake, low-grade systemic inflammation and metabolic changes associated with this diet drive paediatric NAFLD [35,139]. There has also been a significant association with red, but not white, meat. This may be due to the fact that white meat contains less (saturated) fat. The dietary pattern of people consuming predominantly red meat may also differ (e.g., eating fewer vegetables) from those who consume white meat, but not red meat [229,230]. The Mediterranean diet (MD) is considered a healthy and simple diet, and has been suggested by a variety of authors to prevent and treat paediatric NAFLD. There is no single MD, as all countries around the Mediterranean Sea have their own variety of this diet. The frequency by which certain foods and macronutrients are consumed, as well as the beneficial ratios (e.g., omega fatty acids), are as important as the associated lifestyle. Studies generally list the foods, but the lifestyle associated with MD is more relaxed, with more physical work and exercise, as well as having family meals [217–220,248,249]. No studies for vegetarian or vegan dietary trials/interventions in paediatric NAFLD were found.

The main focus on single macronutrients and NAFLD in studies is centred around carbohydrates and especially fructose, sucrose and HFCS. While the majority of consumed calories stem from carbohydrates, the total energy and carbohydrate intake are increased in children with NAFLD [86]. There is, however, a focus on free sugars, which should be limited to 10% of the total daily intake and pose a main issue in developing paediatric NAFLD [85]. Several studies showed that following this recommendation benefits the hepatic fat fraction, and improved metabolic parameters as well as liver enzymes could be achieved. Interestingly, while fructose does not cause NAFLD by itself, intake in a refined form is strongly associated with NAFLD [136,137]. When fructose is consumed in its natural form (e.g., fruit), its constituents (flavanols, epicatechin, ascorbate and other antioxidants) may antagonise the negative effects of fructose [115,116]. A relevant issue is the consumption of sugar-sweetened beverages and energy drinks that contain large amounts of sucrose and high-fructose-corn syrup [105]. In studies, even a several-day-long reduction of fructose led to an improvement in liver health [131,135]. In adults, a single 360 mL/d threshold of soft drink has been reported for metabolic syndrome [147,148]. For NAFLD and especially hepatic fibrosis, a dose-dependent association with soft drink consumption exists. In view of this, a significant reduction in fructose, sucrose and HFCS in processed foods, beverages and a general ban on high-fructose corn syrup are advised [38,87,92,137,145,146,250]. The role of fructose in the intestinal microbiome and gut barrier function remains under debate [120,122].

There is an association between the amount of fat consumed and increased NAFLD-risk, but also of the quality of fat. Saturated fatty acids should be avoided in general. As 90% of ingested fat consists of triglycerides (the rest being phospholipids, sphingolipids, cholesterol and the lipophile vitamins A, D, E and K), the main focus should lie on these. In patients' perception, the role of nutritional cholesterol in metabolic disorders and NAFLD seems overestimated, as only a fraction of ingested cholesterol is absorbed. Patient education should, therefore, aim at MUFAs and PUFAs, as well as the total fat amount and ω -3/ ω -6 ratio. Evidence supports the consumption of a diet rich in ω -3-fatty-acids, while ω -6-fatty acids and SLCFAs should be avoided due to their associations with NAFLD. This further advocates the Mediterranean diet as a therapeutic diet of choice for paediatric NAFLD [46,156,157]. Fat and carbohydrates (especially fructose) exert an additive effect in causing NAFLD in the paediatric population [128,139].

There are limited data on protein and paediatric NAFLD and the results are controversial. Although there are reports of significantly higher intake of protein in NAFLD, there is also evidence that diets low in protein are associated with NAFLD. A possible explanation for the higher intake is that a main source of protein is (red) meat, which is also richer in fat and typically associated with a Western diet. Dietary protein is linked to inflammatory processes, influencing the gut microbiome and NAFLD progression. The depletion of protein, on the other hand, may lead to the reduction of muscle mass, inducing gluconeogenesis via arginine from the muscle and thus lowering the capability for glucose resorption and disturbing the metabolic equilibrium [188–191], while others found no difference [77,192].

5. Conclusions

There are key roles of nutrition and especially macronutrients in the pathogenesis of paediatric NAFLD. Fructose, sucrose, HFCS, saturated fatty acids, trans-fatty acids and ω -6 fatty acids are strongly associated with driving paediatric NAFLD [142,171,186,251,252]. On the other hand, fibre, low-glycaemic-index diets, MUFAs and ω -3 fatty acids are beneficial in the prevention and treatment of paediatric NAFLD [253–256]. There is no evidence supporting children with NAFLD and children with obesity requiring a different nutritional regimen compared with each other and healthy, lean children. Weight normalisation benefits both obesity and NAFLD. As a consequence, the same dietary advice is given to children with NAFLD as to children with obesity. Unfortunately, achieving and maintaining weight loss is very difficult (<10% success over a period of 2 years intervention) [257]. The best

results for childhood weight loss have been achieved by multi-disciplinary family-based behavioural treatment [43]. In meta-analyses, no single diet has been superior in treating paediatric NAFLD [68]. However, the composition of macronutrients in the Mediterranean diet (MD) and certain studies support the MD as suitable for preventing and treating NAFLD [70–73]. The established recommendations of avoiding saturated fatty acids, trans-fatty acids, simple sugars (fructose, sucrose and HFCS) and a high-caloric Western Diet are supported by the literature [258]. Currently, the optimal proportions of total macronutrients (carbohydrate, fat and protein) in the diet of NAFLD-patients are unknown [74]. The role of dietary protein in paediatric NAFLD remains contradictory [156,193,194]. In addition, at the moment, there are no formal recommendations for the treatment of lean NAFLD [64,245]. Table 5 lists the current recommendations as provided by literature research.

Table 5. Conclusions from literature research concerning dietary intervention. (abbreviations: MUFAs (mono-unsaturated fatty acids), HFCS (high-fructose corn syrup)).

Recommended	Avoid
ω -3 fatty acids	Fructose, sucrose and HFCS
ω -3/ ω -6 ratio of 1:1–1:4	Sugar-sweetened beverages
Monounsaturated fatty acids (MUFAs)	Saturated fatty acids
Dietary Fibre	Trans-fatty acids
Eucaloric diet	ω -6 fatty acids
Low glycemic index diet	(Western-style) Hypercaloric diet

More efforts in preventing paediatric NAFLD by dietary education and the avoidance of harmful macronutrients need to be undertaken. It is clear that combining dietary intervention with physical activity is superior to dietary intervention alone. Further studies on the role of macronutrients and optimal dietary intervention in paediatric NAFLD are needed [259–261].

Author Contributions: Conceptualization, T.P., D.F. and D.W.; Methodology, D.W., T.P., A.L. and N.S.; Analysis, T.P., D.F., K.G. and A.M.S.; Writing—Original Draft Preparation, T.P., D.F., V.J. and D.T.; Writing—Review and Editing, T.P., K.M. (Katharina Mörwald), K.M. (Katharina Maruszczak), H.M., J.G. and N.S.; Supervision, D.W.; Project Administration, T.P. and D.F. All authors discussed the results and commented on the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethical review and approval were waived for this study due to the fact that this is a review that is based upon literature research.

Data Availability Statement: All articles' references can be found on the online platform [Pubmed.gov](https://pubmed.ncbi.nlm.nih.gov/).

Acknowledgments: Nicola Moffat for English editing.

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

References

- Marcason, W. What are the current guidelines for pediatric non-alcoholic fatty liver disease? *J. Acad. Nutr. Diet.* **2013**, *113*, 1772. [[CrossRef](#)] [[PubMed](#)]
- Clemente, M.G.; Mandato, C.; Poeta, M.; Vajro, P. Pediatric non-alcoholic fatty liver disease: Recent solutions, unresolved issues, and future research directions. *World J. Gastroenterol.* **2016**, *22*, 8078–8093. [[CrossRef](#)] [[PubMed](#)]
- Schwimmer, J.B.; Deutsch, R.; Kahen, T.; Lavine, J.E.; Stanley, C.; Behling, C. Prevalence of fatty liver in children and adolescents. *Pediatrics* **2006**, *118*, 1388–1393. [[CrossRef](#)]
- Berardis, S.; Sokal, E. Pediatric non-alcoholic fatty liver disease: An increasing public health issue. *Eur. J. Pediatr.* **2014**, *173*, 131–139. [[CrossRef](#)]
- Nobili, V.; Alisi, A.; Newton, K.P.; Schwimmer, J.B. Comparison of the Phenotype and Approach to Pediatric vs. Adult Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* **2016**, *150*, 1798–1810. [[CrossRef](#)] [[PubMed](#)]
- Younossi, Z.M.; Koenig, A.B.; Abdelatif, D.; Fazel, Y.; Henry, L.; Wymer, M. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* **2016**, *64*, 73–84. [[CrossRef](#)]

7. Ratziu, V.; Bellentani, S.; Cortez-Pinto, H.; Day, C.; Marchesini, G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J. Hepatol.* **2010**, *53*, 372–384. [[CrossRef](#)]
8. Patton, H.M.; Lavine, J.E.; Van Natta, M.L.; Schwimmer, J.B.; Kleiner, D.; Molleston, J.; Network, N.S.C.R. Clinical correlates of histopathology in pediatric nonalcoholic steatohepatitis. *Gastroenterology* **2008**, *135*, 1961–1971.e1962. [[CrossRef](#)]
9. Carter-Kent, C.; Brunt, E.M.; Yerian, L.M.; Alkhoury, N.; Angulo, P.; Kohli, R.; Ling, S.C.; Xanthakos, S.A.; Whittington, P.F.; Charatcharoenwitthaya, P.; et al. Relations of steatosis type, grade, and zonality to histological features in pediatric nonalcoholic fatty liver disease. *J. Pediatr. Gastroenterol. Nutr.* **2011**, *52*, 190–197. [[CrossRef](#)]
10. Anderson, E.L.; Howe, L.D.; Jones, H.E.; Higgins, J.P.; Lawlor, D.A.; Fraser, A. The Prevalence of Non-Alcoholic Fatty Liver Disease in Children and Adolescents: A Systematic Review and Meta-Analysis. *PLoS ONE* **2015**, *10*, e0140908. [[CrossRef](#)]
11. Conjeevaram Selvakumar, P.K.; Kabbany, M.N.; Lopez, R.; Rayas, M.S.; Lynch, J.L.; Alkhoury, N. Prevalence of Suspected Nonalcoholic Fatty Liver Disease in Lean Adolescents in the United States. *J. Pediatr. Gastroenterol. Nutr.* **2018**, *67*, 75–79. [[CrossRef](#)] [[PubMed](#)]
12. Ozhan, B.; Ersoy, B.; Kiremitci, S.; Ozkol, M.; Taneli, F. Insulin sensitivity indices: Fasting versus glucose-stimulated indices in pediatric non-alcoholic fatty liver disease. *Eur. Rev. Med. Pharmacol. Sci.* **2015**, *19*, 3450–3458. [[PubMed](#)]
13. Morandi, A.; Di Sessa, A.; Zusi, C.; Umano, G.R.; El Mazloum, D.; Fornari, E.; Miraglia Del Giudice, E.; Targher, G.; Maffei, C. Nonalcoholic Fatty Liver Disease and Estimated Insulin Resistance in Obese Youth: A Mendelian Randomization Analysis. *J. Clin. Endocrinol. Metab.* **2020**, *105*, e4046–e4054. [[CrossRef](#)] [[PubMed](#)]
14. Gastaldelli, A. Insulin resistance and reduced metabolic flexibility: Cause or consequence of NAFLD? *Clin. Sci.* **2017**, *131*, 2701–2704. [[CrossRef](#)]
15. Byrne, C.D.; Targher, G. NAFLD: A multisystem disease. *J. Hepatol.* **2015**, *62*, S47–S64. [[CrossRef](#)]
16. Draijer, L.; Benninga, M.; Koot, B. Pediatric NAFLD: An overview and recent developments in diagnostics and treatment. *Expert Rev. Gastroenterol. Hepatol.* **2019**, *13*, 447–461. [[CrossRef](#)] [[PubMed](#)]
17. Patton, H.M.; Yates, K.; Unalp-Arida, A.; Behling, C.A.; Huang, T.T.; Rosenthal, P.; Sanyal, A.J.; Schwimmer, J.B.; Lavine, J.E. Association between metabolic syndrome and liver histology among children with nonalcoholic Fatty liver disease. *Am. J. Gastroenterol.* **2010**, *105*, 2093–2102. [[CrossRef](#)]
18. Sundaram, S.S.; Zeitler, P.; Nadeau, K. The metabolic syndrome and nonalcoholic fatty liver disease in children. *Curr. Opin. Pediatr.* **2009**, *21*, 529–535. [[CrossRef](#)]
19. Fabbrini, E.; Sullivan, S.; Klein, S. Obesity and nonalcoholic fatty liver disease: Biochemical, metabolic, and clinical implications. *Hepatology* **2010**, *51*, 679–689. [[CrossRef](#)]
20. Pacifico, L.; Nobili, V.; Anania, C.; Verdecchia, P.; Chiesa, C. Pediatric nonalcoholic fatty liver disease, metabolic syndrome and cardiovascular risk. *World J. Gastroenterol.* **2011**, *17*, 3082–3091. [[CrossRef](#)] [[PubMed](#)]
21. Pacifico, L.; Chiesa, C.; Anania, C.; De Merulis, A.; Osborn, J.F.; Romaggioli, S.; Gaudio, E. Nonalcoholic fatty liver disease and the heart in children and adolescents. *World J. Gastroenterol.* **2014**, *20*, 9055–9071. [[CrossRef](#)] [[PubMed](#)]
22. Pacifico, L.; Bonci, E.; Andreoli, G.M.; Di Martino, M.; Gallozzi, A.; De Luca, E.; Chiesa, C. The Impact of Nonalcoholic Fatty Liver Disease on Renal Function in Children with Overweight/Obesity. *Int. J. Mol. Sci.* **2016**, *17*, 1218. [[CrossRef](#)] [[PubMed](#)]
23. Pardee, P.E.; Dunn, W.; Schwimmer, J.B. Non-alcoholic fatty liver disease is associated with low bone mineral density in obese children. *Aliment. Pharmacol. Ther.* **2012**, *35*, 248–254. [[CrossRef](#)]
24. Newton, K.P.; Hou, J.; Crimmins, N.A.; Lavine, J.E.; Barlow, S.E.; Xanthakos, S.A.; Africa, J.; Behling, C.; Donithan, M.; Clark, J.M.; et al. Prevalence of Prediabetes and Type 2 Diabetes in Children With Nonalcoholic Fatty Liver Disease. *JAMA Pediatr.* **2016**, *170*, e161971. [[CrossRef](#)]
25. Verhulst, S.L.; Jacobs, S.; Aerts, L.; Schrauwen, N.; Haentjens, D.; Rooman, R.P.; Gaal, L.V.; De Backer, W.A.; Desager, K.N. Sleep-disordered breathing: A new risk factor of suspected fatty liver disease in overweight children and adolescents? *Sleep Breath* **2009**, *13*, 207–210. [[CrossRef](#)]
26. Ayonrinde, O.T.; Adams, L.A.; Doherty, D.A.; Mori, T.A.; Beilin, L.J.; Oddy, W.H.; Hickey, M.; Sloboda, D.M.; Olynyk, J.K.; Hart, R. Adverse metabolic phenotype of adolescent girls with non-alcoholic fatty liver disease plus polycystic ovary syndrome compared with other girls and boys. *J. Gastroenterol. Hepatol.* **2016**, *31*, 980–987. [[CrossRef](#)]
27. Armstrong, M.J.; Adams, L.A.; Canbay, A.; Syn, W.K. Extrahepatic complications of nonalcoholic fatty liver disease. *Hepatology* **2014**, *59*, 1174–1197. [[CrossRef](#)] [[PubMed](#)]
28. Masuzaki, R.; Karp, S.J.; Omata, M. NAFLD as a risk factor for HCC: New rules of engagement? *Hepatol. Int.* **2016**, *10*, 533–534. [[CrossRef](#)] [[PubMed](#)]
29. Targher, G.; Day, C.P.; Bonora, E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N. Engl. J. Med.* **2010**, *363*, 1341–1350. [[CrossRef](#)]
30. Goyal, N.P.; Schwimmer, J.B. The Progression and Natural History of Pediatric Nonalcoholic Fatty Liver Disease. *Clin. Liver Dis.* **2016**, *20*, 325–338. [[CrossRef](#)]
31. Schwimmer, J.B.; Behling, C.; Newbury, R.; Deutsch, R.; Nievergelt, C.; Schork, N.J.; Lavine, J.E. Histopathology of pediatric nonalcoholic fatty liver disease. *Hepatology* **2005**, *42*, 641–649. [[CrossRef](#)]
32. Feldstein, A.E.; Charatcharoenwitthaya, P.; Treeprasertsuk, S.; Benson, J.T.; Enders, F.B.; 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. [[CrossRef](#)]

33. Vittorio, J.; Lavine, J.E. Recent advances in understanding and managing pediatric nonalcoholic fatty liver disease. *F1000Res* **2020**, *9*, 377. [[CrossRef](#)] [[PubMed](#)]
34. Manco, M.; Bedogni, G.; Marcellini, M.; Devito, R.; Ciampalini, P.; Sartorelli, M.R.; Comparcola, D.; Piemonte, F.; Nobili, V. Waist circumference correlates with liver fibrosis in children with non-alcoholic steatohepatitis. *Gut* **2008**, *57*, 1283–1287. [[CrossRef](#)] [[PubMed](#)]
35. Oddy, W.H.; Herbison, C.E.; Jacoby, P.; Ambrosini, G.L.; O’Sullivan, T.A.; Ayonrinde, O.T.; Olynyk, J.K.; Black, L.J.; Beilin, L.J.; Mori, T.A.; et al. The Western dietary pattern is prospectively associated with nonalcoholic fatty liver disease in adolescence. *Am. J. Gastroenterol.* **2013**, *108*, 778–785. [[CrossRef](#)]
36. Hattar, L.N.; Wilson, T.A.; Tabotabo, L.A.; Smith, E.O.; Abrams, S.H. Physical activity and nutrition attitudes in obese Hispanic children with non-alcoholic steatohepatitis. *World J. Gastroenterol.* **2011**, *17*, 4396–4403. [[CrossRef](#)]
37. Assy, N.; Nasser, G.; Kamayse, I.; Nseir, W.; Beniashvili, Z.; Djibre, A.; Grosovski, M. Soft drink consumption linked with fatty liver in the absence of traditional risk factors. *Can. J. Gastroenterol.* **2008**, *22*, 811–816. [[CrossRef](#)]
38. Ouyang, X.; Cirillo, P.; Sautin, Y.; McCall, S.; Bruchette, J.L.; Diehl, A.M.; Johnson, R.J.; Abdelmalek, M.F. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. *J. Hepatol.* **2008**, *48*, 993–999. [[CrossRef](#)]
39. He, S.; McPhaul, C.; Li, J.Z.; Garuti, R.; Kinch, L.; Grishin, N.V.; Cohen, J.C.; Hobbs, H.H. A sequence variation (I148M) in PNPLA3 associated with nonalcoholic fatty liver disease disrupts triglyceride hydrolysis. *J. Biol. Chem.* **2010**, *285*, 6706–6715. [[CrossRef](#)]
40. Kumari, M.; Schoiswohl, G.; Chitruja, C.; Paar, M.; Cornaciu, I.; Rangrez, A.Y.; Wongsiriroj, N.; Nagy, H.M.; Ivanova, P.T.; Scott, S.A.; et al. Adiponutrin functions as a nutritionally regulated lysophosphatidic acid acyltransferase. *Cell Metab.* **2012**, *15*, 691–702. [[CrossRef](#)] [[PubMed](#)]
41. Mangge, H.; Baumgartner, B.G.; Zelzer, S.; Prüller, F.; Schnedl, W.J.; Reininghaus, E.Z.; Haybaeck, J.; Lackner, C.; Stauber, R.; Aigner, E.; et al. Patatin-like phospholipase 3 (rs738409) gene polymorphism is associated with increased liver enzymes in obese adolescents and metabolic syndrome in all ages. *Aliment. Pharmacol. Ther.* **2015**, *42*, 99–105. [[CrossRef](#)]
42. Uygun, A.; Ozturk, K.; Demirci, H.; Oztuna, A.; Eren, F.; Kozan, S.; Yilmaz, Y.; Kurt, O.; Turker, T.; Vatanserver, S.; et al. The association of nonalcoholic fatty liver disease with genetic polymorphisms: A multicenter study. *Eur. J. Gastroenterol. Hepatol.* **2017**, *29*, 441–447. [[CrossRef](#)]
43. 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. *Nutr. Res.* **2018**, *58*, 1–16. [[CrossRef](#)] [[PubMed](#)]
44. Dongiovanni, P.; Valenti, L.; Rametta, R.; Daly, A.K.; Nobili, V.; Mozzi, E.; Leathart, J.B.; Pietrobattista, A.; Burt, A.D.; Maggioni, M.; et al. Genetic variants regulating insulin receptor signalling are associated with the severity of liver damage in patients with non-alcoholic fatty liver disease. *Gut* **2010**, *59*, 267–273. [[CrossRef](#)]
45. Santoro, N.; Zhang, C.K.; Zhao, H.; Pakstis, A.J.; Kim, G.; Kursawe, R.; Dykas, D.J.; Bale, A.E.; Giannini, C.; Pierpont, B.; et al. Variant in the glucokinase regulatory protein (GCKR) gene is associated with fatty liver in obese children and adolescents. *Hepatology* **2012**, *55*, 781–789. [[CrossRef](#)] [[PubMed](#)]
46. Bonsembiante, L.; Targher, G.; Maffei, C. Non-alcoholic fatty liver disease in obese children and adolescents: A role for nutrition? *Eur. J. Clin. Nutr.* **2022**, *76*, 28–39. [[CrossRef](#)]
47. Barker, D.J. The fetal and infant origins of disease. *Eur. J. Clin. Investig.* **1995**, *25*, 457–463. [[CrossRef](#)]
48. Bertrando, S.; Vajro, P. NAFLD at the Interface of the Mother-Infant Dyad. *Curr. Pharm. Des.* **2020**, *26*, 1119–1125. [[CrossRef](#)]
49. Newton, K.P.; Feldman, H.S.; Chambers, C.D.; Wilson, L.; Behling, C.; Clark, J.M.; Molleston, J.P.; Chalasani, N.; Sanyal, A.J.; Fishbein, M.H.; et al. Low and High Birth Weights Are Risk Factors for Nonalcoholic Fatty Liver Disease in Children. *J. Pediatr.* **2017**, *187*, 141–146.e141. [[CrossRef](#)] [[PubMed](#)]
50. Kong, L.; Lu, Y.; Zhang, S.; Nan, Y.; Qiao, L. Role of nutrition, gene polymorphism, and gut microbiota in non-alcoholic fatty liver disease. *Discov. Med.* **2017**, *24*, 95–106. [[PubMed](#)]
51. Modi, N.; Murgasova, D.; Ruager-Martin, R.; Thomas, E.L.; Hyde, M.J.; Gale, C.; Santhakumaran, S.; Doré, C.J.; Alavi, A.; Bell, J.D. The influence of maternal body mass index on infant adiposity and hepatic lipid content. *Pediatr. Res.* **2011**, *70*, 287–291. [[CrossRef](#)] [[PubMed](#)]
52. Brumbaugh, D.E.; Friedman, J.E. Developmental origins of nonalcoholic fatty liver disease. *Pediatr. Res.* **2014**, *75*, 140–147. [[CrossRef](#)] [[PubMed](#)]
53. Goran, M.I.; Dumke, K.; Bouret, S.G.; Kayser, B.; Walker, R.W.; Blumberg, B. The obesogenic effect of high fructose exposure during early development. *Nat. Rev. Endocrinol.* **2013**, *9*, 494–500. [[CrossRef](#)]
54. Sloboda, D.M.; Li, M.; Patel, R.; Clayton, Z.E.; Yap, C.; Vickers, M.H. Early life exposure to fructose and offspring phenotype: Implications for long term metabolic homeostasis. *J. Obes.* **2014**, *2014*, 203474. [[CrossRef](#)]
55. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J. Hepatol.* **2016**, *64*, 1388–1402. [[CrossRef](#)] [[PubMed](#)]
56. Chalasani, N.; Younossi, Z.; Lavine, J.E.; Diehl, A.M.; Brunt, E.M.; Cusi, K.; Charlton, M.; Sanyal, A.J. The diagnosis and management of non-alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* **2012**, *55*, 2005–2023. [[CrossRef](#)] [[PubMed](#)]

57. Africa, J.A.; Newton, K.P.; Schwimmer, J.B. Lifestyle Interventions Including Nutrition, Exercise, and Supplements for Nonalcoholic Fatty Liver Disease in Children. *Dig. Dis. Sci.* **2016**, *61*, 1375–1386. [[CrossRef](#)]
58. Roeb, E.; Steffen, H.M.; Bantel, H.; Baumann, U.; Canbay, A.; Demir, M.; Drebber, U.; Geier, A.; Hampe, J.; Hellerbrand, C.; et al. S2k Guideline non-alcoholic fatty liver disease. *Z. Gastroenterol.* **2015**, *53*, 668–723. [[CrossRef](#)] [[PubMed](#)]
59. Koopman, K.E.; Caan, M.W.; Nederveen, A.J.; Pels, A.; Ackermans, M.T.; Fliers, E.; la Fleur, S.E.; Serlie, M.J. Hypercaloric diets with increased meal frequency, but not meal size, increase intrahepatic triglycerides: A randomized controlled trial. *Hepatology* **2014**, *60*, 545–553. [[CrossRef](#)]
60. Malik, V.S.; Popkin, B.M.; Bray, G.A.; Després, J.P.; Willett, W.C.; Hu, F.B. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: A meta-analysis. *Diabetes Care* **2010**, *33*, 2477–2483. [[CrossRef](#)]
61. Te Morenga, L.; Mallard, S.; Mann, J. Dietary sugars and body weight: Systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ* **2012**, *346*, e7492. [[CrossRef](#)] [[PubMed](#)]
62. Johnson, R.K.; Appel, L.J.; Brands, M.; Howard, B.V.; Lefevre, M.; Lustig, R.H.; Sacks, F.; Steffen, L.M.; Wylie-Rosett, J.; American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism and the Council on Epidemiology and Prevention; et al. Dietary sugars intake and cardiovascular health: A scientific statement from the American Heart Association. *Circulation* **2009**, *120*, 1011–1020. [[CrossRef](#)] [[PubMed](#)]
63. Feldstein, A.E.; Patton-Ku, D.; Boutelle, K.N. Obesity, nutrition, and liver disease in children. *Clin. Liver Dis.* **2014**, *18*, 219–231. [[CrossRef](#)]
64. Chalasani, N.; Younossi, Z.; Lavine, J.E.; Charlton, M.; Cusi, K.; Rinella, M.; Harrison, S.A.; Brunt, E.M.; Sanyal, A.J. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* **2018**, *67*, 328–357. [[CrossRef](#)] [[PubMed](#)]
65. Mameli, C.; Zuccotti, G.V.; Carnovale, C.; Galli, E.; Nannini, P.; Cervia, D.; Perrotta, C. An update on the assessment and management of metabolic syndrome, a growing medical emergency in paediatric populations. *Pharmacol. Res.* **2017**, *119*, 99–117. [[CrossRef](#)] [[PubMed](#)]
66. van der Heijden, L.B.; Feskens, E.J.M.; Janse, A.J. Maintenance interventions for overweight or obesity in children: A systematic review and meta-analysis. *Obes. Rev.* **2018**, *19*, 798–809. [[CrossRef](#)]
67. Gidding, S.S.; Dennison, B.A.; Birch, L.L.; Daniels, S.R.; Gillman, M.W.; Gilman, M.W.; Lichtenstein, A.H.; Rattay, K.T.; Steinberger, J.; Stettler, N.; et al. Dietary recommendations for children and adolescents: A guide for practitioners: Consensus statement from the American Heart Association. *Circulation* **2005**, *112*, 2061–2075. [[CrossRef](#)]
68. Gibson, P.S.; Lang, S.; Dhawan, A.; Fitzpatrick, E.; Blumfield, M.L.; Truby, H.; Hart, K.H.; Moore, J.B. Systematic Review: Nutrition and Physical Activity in the Management of Paediatric Nonalcoholic Fatty Liver Disease. *J. Pediatr. Gastroenterol. Nutr.* **2017**, *65*, 141–149. [[CrossRef](#)] [[PubMed](#)]
69. Mouzaki, M.; Allard, J.P. The role of nutrients in the development, progression, and treatment of nonalcoholic fatty liver disease. *J. Clin. Gastroenterol.* **2012**, *46*, 457–467. [[CrossRef](#)]
70. Della Corte, C.; Mosca, A.; Vania, A.; Alterio, A.; Iasevoli, S.; Nobili, V. Good adherence to the Mediterranean diet reduces the risk for NASH and diabetes in pediatric patients with obesity: The results of an Italian Study. *Nutrition* **2017**, *39–40*, 8–14. [[CrossRef](#)]
71. Buckland, G.; Bach, A.; Serra-Majem, L. Obesity and the Mediterranean diet: A systematic review of observational and intervention studies. *Obes. Rev.* **2008**, *9*, 582–593. [[CrossRef](#)]
72. Farajian, P.; Risvas, G.; Karasouli, K.; Pounis, G.D.; Kastorini, C.M.; Panagiotakos, D.B.; Zampelas, A. Very high childhood obesity prevalence and low adherence rates to the Mediterranean diet in Greek children: The GRECO study. *Atherosclerosis* **2011**, *217*, 525–530. [[CrossRef](#)] [[PubMed](#)]
73. Kabaran, S.; Gezer, C. Determination of the Mediterranean Diet and the obesity status of children and adolescents in Turkish Republic of Northern Cyprus. *Turk. J. Pediatr. Dis.* **2013**, *7*, 11–20. [[CrossRef](#)]
74. Eslamparast, T.; Tandon, P.; Raman, M. Dietary Composition Independent of Weight Loss in the Management of Non-Alcoholic Fatty Liver Disease. *Nutrients* **2017**, *9*, 800. [[CrossRef](#)] [[PubMed](#)]
75. Mitchel, E.B.; Lavine, J.E. Review article: The management of paediatric nonalcoholic fatty liver disease. *Aliment. Pharmacol. Ther.* **2014**, *40*, 1155–1170. [[CrossRef](#)]
76. Goss, A.M.; Dowla, S.; Pendergrass, M.; Ashraf, A.; Bolding, M.; Morrison, S.; Amerson, A.; Soleymani, T.; Gower, B. Effects of a carbohydrate-restricted diet on hepatic lipid content in adolescents with non-alcoholic fatty liver disease: A pilot, randomized trial. *Pediatr. Obes.* **2020**, *15*, e12630. [[CrossRef](#)]
77. Musso, G.; Gambino, R.; De Michieli, F.; Cassader, M.; Rizzetto, M.; Durazzo, M.; Fagà, E.; Silli, B.; Pagano, G. Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis. *Hepatology* **2003**, *37*, 909–916. [[CrossRef](#)]
78. Yasutake, K.; Nakamuta, M.; Shima, Y.; Ohyama, A.; Masuda, K.; Haruta, N.; Fujino, T.; Aoyagi, Y.; Fukuizumi, K.; Yoshimoto, T.; et al. Nutritional investigation of non-obese patients with non-alcoholic fatty liver disease: The significance of dietary cholesterol. *Scand. J. Gastroenterol.* **2009**, *44*, 471–477. [[CrossRef](#)] [[PubMed](#)]
79. Mager, D.R.; Iñiguez, I.R.; Gilmour, S.; Yap, J. The effect of a low fructose and low glycemic index/load (FRAGILE) dietary intervention on indices of liver function, cardiometabolic risk factors, and body composition in children and adolescents with nonalcoholic fatty liver disease (NAFLD). *JPEN J. Parenter. Enter. Nutr.* **2015**, *39*, 73–84. [[CrossRef](#)]
80. Putignani, L.; Dallapiccola, B. Foodomics as part of the host-microbiota-exposome interplay. *J. Proteom.* **2016**, *147*, 3–20. [[CrossRef](#)]

81. Del Chierico, F.; Nobili, V.; Vernocchi, P.; Russo, A.; De Stefanis, C.; Gnani, D.; Furlanello, C.; Zandonà, A.; Paci, P.; Capuani, G.; et al. Gut microbiota profiling of pediatric nonalcoholic fatty liver disease and obese patients unveiled by an integrated meta-omics-based approach. *Hepatology* **2017**, *65*, 451–464. [[CrossRef](#)] [[PubMed](#)]
82. Vos, M.B.; Colvin, R.; Belt, P.; Molleston, J.P.; Murray, K.F.; Rosenthal, P.; Schwimmer, J.B.; Tonascia, J.; Unalp, A.; Lavine, J.E.; et al. Correlation of vitamin E, uric acid, and diet composition with histologic features of pediatric NAFLD. *J. Pediatr. Gastroenterol. Nutr.* **2012**, *54*, 90–96. [[CrossRef](#)]
83. Anderson, E.L.; Howe, L.D.; Fraser, A.; Macdonald-Wallis, C.; Callaway, M.P.; Sattar, N.; Day, C.; Tilling, K.; Lawlor, D.A. Childhood energy intake is associated with nonalcoholic fatty liver disease in adolescents. *J. Nutr.* **2015**, *145*, 983–989. [[CrossRef](#)] [[PubMed](#)]
84. Gibson, P.S.; Lang, S.; Gilbert, M.; Kamat, D.; Bansal, S.; Ford-Adams, M.E.; Desai, A.P.; Dhawan, A.; Fitzpatrick, E.; Moore, J.B.; et al. Assessment of Diet and Physical Activity in Paediatric Non-Alcoholic Fatty Liver Disease Patients: A United Kingdom Case Control Study. *Nutrients* **2015**, *7*, 9721–9733. [[CrossRef](#)]
85. World Health Organization. *Guideline: Sugars Intake for Adults and Children*; World Health Organization: Geneva, Switzerland, 2015.
86. Nier, A.; Brandt, A.; Conzelmann, I.B.; Özel, Y.; Bergheim, I. Non-Alcoholic Fatty Liver Disease in Overweight Children: Role of Fructose Intake and Dietary Pattern. *Nutrients* **2018**, *10*, 1329. [[CrossRef](#)] [[PubMed](#)]
87. Lim, J.S.; Mietus-Snyder, M.; Valente, A.; Schwarz, J.M.; Lustig, R.H. The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. *Nat. Rev. Gastroenterol. Hepatol.* **2010**, *7*, 251–264. [[CrossRef](#)] [[PubMed](#)]
88. Starling, A.P.; Sauder, K.A.; Kaar, J.L.; Shapiro, A.L.; Siega-Riz, A.M.; Dabelea, D. Maternal Dietary Patterns during Pregnancy Are Associated with Newborn Body Composition. *J. Nutr.* **2017**, *147*, 1334–1339. [[CrossRef](#)]
89. Lee, W.C.; Wu, K.L.H.; Leu, S.; Tain, Y.L. Translational insights on developmental origins of metabolic syndrome: Focus on fructose consumption. *Biomed. J.* **2018**, *41*, 96–101. [[CrossRef](#)]
90. Rodríguez, L.A.; Madsen, K.A.; Cotterman, C.; Lustig, R.H. Added sugar intake and metabolic syndrome in US adolescents: Cross-sectional analysis of the National Health and Nutrition Examination Survey 2005–2012. *Public Health Nutr.* **2016**, *19*, 2424–2434. [[CrossRef](#)]
91. Jensen, T.; Abdelmalek, M.F.; Sullivan, S.; Nadeau, K.J.; Green, M.; Roncal, C.; Nakagawa, T.; Kuwabara, M.; Sato, Y.; Kang, D.H.; et al. Fructose and sugar: A major mediator of non-alcoholic fatty liver disease. *J. Hepatol.* **2018**, *68*, 1063–1075. [[CrossRef](#)]
92. Dekker, M.J.; Su, Q.; Baker, C.; Rutledge, A.C.; Adeli, K. Fructose: A highly lipogenic nutrient implicated in insulin resistance, hepatic steatosis, and the metabolic syndrome. *Am. J. Physiol. Endocrinol. Metab.* **2010**, *299*, E685–E694. [[CrossRef](#)]
93. Zúñiga, J.; Cancino, M.; Medina, F.; Varela, P.; Vargas, R.; Tapia, G.; Videla, L.A.; Fernández, V. N-3 PUFA supplementation triggers PPAR- α activation and PPAR- α /NF- κ B interaction: Anti-inflammatory implications in liver ischemia-reperfusion injury. *PLoS ONE* **2011**, *6*, e28502. [[CrossRef](#)]
94. Nobili, V.; Marcellini, M.; Devito, R.; Ciampalini, P.; Piemonte, F.; Comparcola, D.; Sartorelli, M.R.; Angulo, P. NAFLD in children: A prospective clinical-pathological study and effect of lifestyle advice. *Hepatology* **2006**, *44*, 458–465. [[CrossRef](#)] [[PubMed](#)]
95. Neuschwander-Tetri, B.A. Carbohydrate intake and nonalcoholic fatty liver disease. *Curr. Opin. Clin. Nutr. Metab. Care* **2013**, *16*, 446–452. [[CrossRef](#)] [[PubMed](#)]
96. Fang, Y.L.; Chen, H.; Wang, C.L.; Liang, L. Pathogenesis of non-alcoholic fatty liver disease in children and adolescence: From “two hit theory” to “multiple hit model”. *World J. Gastroenterol.* **2018**, *24*, 2974–2983. [[CrossRef](#)]
97. Mandala, A.; Janssen, R.C.; Palle, S.; Short, K.R.; Friedman, J.E. Pediatric Non-Alcoholic Fatty Liver Disease: Nutritional Origins and Potential Molecular Mechanisms. *Nutrients* **2020**, *12*, 3166. [[CrossRef](#)]
98. Softic, S.; Gupta, M.K.; Wang, G.X.; Fujisaka, S.; O’Neill, B.T.; Rao, T.N.; Willoughby, J.; Harbison, C.; Fitzgerald, K.; Ilkayeva, O.; et al. Divergent effects of glucose and fructose on hepatic lipogenesis and insulin signaling. *J. Clin. Investig.* **2017**, *127*, 4059–4074. [[CrossRef](#)]
99. Softic, S.; Meyer, J.G.; Wang, G.X.; Gupta, M.K.; Batista, T.M.; Lauritzen, H.P.M.M.; Fujisaka, S.; Serra, D.; Herrero, L.; Willoughby, J.; et al. Dietary Sugars Alter Hepatic Fatty Acid Oxidation via Transcriptional and Post-translational Modifications of Mitochondrial Proteins. *Cell Metab.* **2019**, *30*, 735–753.e734. [[CrossRef](#)] [[PubMed](#)]
100. Schugar, R.C.; Crawford, P.A. Low-carbohydrate ketogenic diets, glucose homeostasis, and nonalcoholic fatty liver disease. *Curr. Opin. Clin. Nutr. Metab. Care* **2012**, *15*, 374–380. [[CrossRef](#)]
101. Browning, J.D.; Baker, J.A.; Rogers, T.; Davis, J.; Satapati, S.; Burgess, S.C. Short-term weight loss and hepatic triglyceride reduction: Evidence of a metabolic advantage with dietary carbohydrate restriction. *Am. J. Clin. Nutr.* **2011**, *93*, 1048–1052. [[CrossRef](#)]
102. Foster, G.D.; Wyatt, H.R.; Hill, J.O.; Makris, A.P.; Rosenbaum, D.L.; Brill, C.; Stein, R.I.; Mohammed, B.S.; Miller, B.; Rader, D.J.; et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: A randomized trial. *Ann. Intern. Med.* **2010**, *153*, 147–157. [[CrossRef](#)]
103. Hu, T.; Mills, K.T.; Yao, L.; Demanelis, K.; Eloustaz, M.; Yancy, W.S.; Kelly, T.N.; He, J.; Bazzano, L.A. Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: A meta-analysis of randomized controlled clinical trials. *Am. J. Epidemiol.* **2012**, *176* (Suppl. 7), S44–S54. [[CrossRef](#)]
104. Schwimmer, J.B.; Ugalde-Nicalo, P.; Welsh, J.A.; Angeles, J.E.; Cordero, M.; Harlow, K.E.; Alazraki, A.; Durelle, J.; Knight-Scott, J.; Newton, K.P.; et al. Effect of a Low Free Sugar Diet vs. Usual Diet on Nonalcoholic Fatty Liver Disease in Adolescent Boys: A Randomized Clinical Trial. *JAMA* **2019**, *321*, 256–265. [[CrossRef](#)]

105. Ventura, E.E.; Davis, J.N.; Goran, M.I. Sugar content of popular sweetened beverages based on objective laboratory analysis: Focus on fructose content. *Obesity* **2011**, *19*, 868–874. [[CrossRef](#)] [[PubMed](#)]
106. Vos, M.B.; Kimmons, J.E.; Gillespie, C.; Welsh, J.; Blanck, H.M. Dietary fructose consumption among US children and adults: The Third National Health and Nutrition Examination Survey. *Medscape J. Med.* **2008**, *10*, 160.
107. Lanaspá, M.A.; Sanchez-Lozada, L.G.; Choi, Y.J.; Cicerchi, C.; Kanbay, M.; Roncal-Jimenez, C.A.; Ishimoto, T.; Li, N.; Marek, G.; Duranay, M.; et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: Potential role in fructose-dependent and -independent fatty liver. *J. Biol. Chem.* **2012**, *287*, 40732–40744. [[CrossRef](#)] [[PubMed](#)]
108. Lanaspá, M.A.; Cicerchi, C.; Garcia, G.; Li, N.; Roncal-Jimenez, C.A.; Rivard, C.J.; Hunter, B.; Andrés-Hernando, A.; Ishimoto, T.; Sánchez-Lozada, L.G.; et al. Counteracting roles of AMP deaminase and AMP kinase in the development of fatty liver. *PLoS ONE* **2012**, *7*, e48801. [[CrossRef](#)] [[PubMed](#)]
109. Cicerchi, C.; Li, N.; Kratzer, J.; Garcia, G.; Roncal-Jimenez, C.A.; Tanabe, K.; Hunter, B.; Rivard, C.J.; Sautin, Y.Y.; Gaucher, E.A.; et al. Uric acid-dependent inhibition of AMP kinase induces hepatic glucose production in diabetes and starvation: Evolutionary implications of the uricase loss in hominids. *FASEB J.* **2014**, *28*, 3339–3350. [[CrossRef](#)]
110. Shapiro, A.; Mu, W.; Roncal, C.; Cheng, K.Y.; Johnson, R.J.; Scarpance, P.J. Fructose-induced leptin resistance exacerbates weight gain in response to subsequent high-fat feeding. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2008**, *295*, R1370–R1375. [[CrossRef](#)]
111. Shapiro, A.; Tümer, N.; Gao, Y.; Cheng, K.Y.; Scarpance, P.J. Prevention and reversal of diet-induced leptin resistance with a sugar-free diet despite high fat content. *Br. J. Nutr.* **2011**, *106*, 390–397. [[CrossRef](#)]
112. Collino, M. High dietary fructose intake: Sweet or bitter life? *World J. Diabetes* **2011**, *2*, 77–81. [[CrossRef](#)] [[PubMed](#)]
113. Bray, G.A.; Popkin, B.M. Calorie-sweetened beverages and fructose: What have we learned 10 years later. *Pediatr. Obes.* **2013**, *8*, 242–248. [[CrossRef](#)]
114. Abid, A.; Taha, O.; Nseir, W.; Farah, R.; Grosovski, M.; Assy, N. Soft drink consumption is associated with fatty liver disease independent of metabolic syndrome. *J. Hepatol.* **2009**, *51*, 918–924. [[CrossRef](#)]
115. Kanerva, N.; Sandboge, S.; Kaartinen, N.E.; Männistö, S.; Eriksson, J.G. Higher fructose intake is inversely associated with risk of nonalcoholic fatty liver disease in older Finnish adults. *Am. J. Clin. Nutr.* **2014**, *100*, 1133–1138. [[CrossRef](#)] [[PubMed](#)]
116. Vasdev, S.; Gill, V.; Parai, S.; Longerich, L.; Gadag, V. Dietary vitamin E and C supplementation prevents fructose induced hypertension in rats. *Mol. Cell. Biochem.* **2002**, *241*, 107–114. [[CrossRef](#)] [[PubMed](#)]
117. Sullivan, J.S.; Le, M.T.; Pan, Z.; Rivard, C.; Love-Osborne, K.; Robbins, K.; Johnson, R.J.; Sokol, R.J.; Sundaram, S.S. Oral fructose absorption in obese children with non-alcoholic fatty liver disease. *Pediatr. Obes.* **2015**, *10*, 188–195. [[CrossRef](#)] [[PubMed](#)]
118. Spruss, A.; Bergheim, I. Dietary fructose and intestinal barrier: Potential risk factor in the pathogenesis of nonalcoholic fatty liver disease. *J. Nutr. Biochem.* **2009**, *20*, 657–662. [[CrossRef](#)] [[PubMed](#)]
119. Caton, P.W.; Nayuni, N.K.; Khan, N.Q.; Wood, E.G.; Corder, R. Fructose induces gluconeogenesis and lipogenesis through a SIRT1-dependent mechanism. *J. Endocrinol.* **2011**, *208*, 273–283. [[CrossRef](#)]
120. Park, G.; Jung, S.; Wellen, K.E.; Jang, C. The interaction between the gut microbiota and dietary carbohydrates in nonalcoholic fatty liver disease. *Exp. Mol. Med.* **2021**, *53*, 809–822. [[CrossRef](#)]
121. Jones, R.B.; Alderete, T.L.; Kim, J.S.; Millstein, J.; Gilliland, F.D.; Goran, M.I. High intake of dietary fructose in overweight/obese teenagers associated with depletion of. *Gut Microbes* **2019**, *10*, 712–719. [[CrossRef](#)]
122. Alemán, J.O.; Henderson, W.A.; Walker, J.M.; Ronning, A.; Jones, D.R.; Walter, P.J.; Daniel, S.G.; Bittinger, K.; Vaughan, R.; MacArthur, R.; et al. Excess dietary fructose does not alter gut microbiota or permeability in humans: A pilot randomized controlled study. *J. Clin. Transl. Sci.* **2021**, *5*, e143. [[CrossRef](#)] [[PubMed](#)]
123. Sellmann, C.; Priebs, J.; Landmann, M.; Degen, C.; Engstler, A.J.; Jin, C.J.; Gärtner, S.; Spruss, A.; Huber, O.; Bergheim, I. Diets rich in fructose, fat or fructose and fat alter intestinal barrier function and lead to the development of nonalcoholic fatty liver disease over time. *J. Nutr. Biochem.* **2015**, *26*, 1183–1192. [[CrossRef](#)] [[PubMed](#)]
124. Lambertz, J.; Weiskirchen, S.; Landert, S.; Weiskirchen, R. Fructose: A Dietary Sugar in Crosstalk with Microbiota Contributing to the Development and Progression of Non-Alcoholic Liver Disease. *Front. Immunol.* **2017**, *8*, 1159. [[CrossRef](#)]
125. Geidl-Flueck, B.; Hochuli, M.; Németh, Á.; Eberl, A.; Derron, N.; Köfeler, H.C.; Tappy, L.; Berneis, K.; Spinass, G.A.; Gerber, P.A. Fructose- and sucrose- but not glucose-sweetened beverages promote hepatic de novo lipogenesis: A randomized controlled trial. *J. Hepatol.* **2021**, *75*, 46–54. [[CrossRef](#)] [[PubMed](#)]
126. Sánchez-Lozada, L.G.; Mu, W.; Roncal, C.; Sautin, Y.Y.; Abdelmalek, M.; Reungjui, S.; Le, M.; Nakagawa, T.; Lan, H.Y.; Yu, X.; et al. Comparison of free fructose and glucose to sucrose in the ability to cause fatty liver. *Eur. J. Nutr.* **2010**, *49*, 1–9. [[CrossRef](#)]
127. Ishimoto, T.; Lanaspá, M.A.; Rivard, C.J.; Roncal-Jimenez, C.A.; Orlicky, D.J.; Cicerchi, C.; McMahan, R.H.; Abdelmalek, M.F.; Rosen, H.R.; Jackman, M.R.; et al. High-fat and high-sucrose (western) diet induces steatohepatitis that is dependent on fructokinase. *Hepatology* **2013**, *58*, 1632–1643. [[CrossRef](#)]
128. O’Sullivan, T.A.; Oddy, W.H.; Bremner, A.P.; Sherriff, J.L.; Ayonrinde, O.T.; Olynyk, J.K.; Beilin, L.J.; Mori, T.A.; Adams, L.A. Lower fructose intake may help protect against development of nonalcoholic fatty liver in adolescents with obesity. *J. Pediatr. Gastroenterol. Nutr.* **2014**, *58*, 624–631. [[CrossRef](#)]
129. Asgharpour, A.; Cazanave, S.C.; Pacana, T.; Seneshaw, M.; Vincent, R.; Banini, B.A.; Kumar, D.P.; Daita, K.; Min, H.K.; Mirshahi, F.; et al. A diet-induced animal model of non-alcoholic fatty liver disease and hepatocellular cancer. *J. Hepatol.* **2016**, *65*, 579–588. [[CrossRef](#)]

130. Schultz, A.; Neil, D.; Aguila, M.B.; Mandarim-de-Lacerda, C.A. Hepatic adverse effects of fructose consumption independent of overweight/obesity. *Int. J. Mol. Sci.* **2013**, *14*, 21873–21886. [CrossRef]
131. Schwarz, J.M.; Noworolski, S.M.; Erkin-Cakmak, A.; Korn, N.J.; Wen, M.J.; Tai, V.W.; Jones, G.M.; Palii, S.P.; Velasco-Alin, M.; Pan, K.; et al. Effects of Dietary Fructose Restriction on Liver Fat, De Novo Lipogenesis, and Insulin Kinetics in Children with Obesity. *Gastroenterology* **2017**, *153*, 743–752. [CrossRef]
132. Jin, R.; Welsh, J.A.; Le, N.A.; Holzberg, J.; Sharma, P.; Martin, D.R.; Vos, M.B. Dietary fructose reduction improves markers of cardiovascular disease risk in Hispanic-American adolescents with NAFLD. *Nutrients* **2014**, *6*, 3187–3201. [CrossRef]
133. Lê, K.A.; Faeh, D.; Stettler, R.; Ith, M.; Kreis, R.; Vermathen, P.; Boesch, C.; Ravussin, E.; Tappy, L. A 4-wk high-fructose diet alters lipid metabolism without affecting insulin sensitivity or ectopic lipids in healthy humans. *Am. J. Clin. Nutr.* **2006**, *84*, 1374–1379. [CrossRef] [PubMed]
134. Lê, K.A.; Ith, M.; Kreis, R.; Faeh, D.; Bortolotti, M.; Tran, C.; Boesch, C.; Tappy, L. Fructose overconsumption causes dyslipidemia and ectopic lipid deposition in healthy subjects with and without a family history of type 2 diabetes. *Am. J. Clin. Nutr.* **2009**, *89*, 1760–1765. [CrossRef] [PubMed]
135. Faeh, D.; Minehira, K.; Schwarz, J.M.; Periasamy, R.; Periasami, R.; Park, S.; Seongsu, P.; Tappy, L. Effect of fructose overfeeding and fish oil administration on hepatic de novo lipogenesis and insulin sensitivity in healthy men. *Diabetes* **2005**, *54*, 1907–1913. [CrossRef] [PubMed]
136. Jin, R.; Le, N.A.; Liu, S.; Farkas Epperson, M.; Ziegler, T.R.; Welsh, J.A.; Jones, D.P.; McClain, C.J.; Vos, M.B. Children with NAFLD are more sensitive to the adverse metabolic effects of fructose beverages than children without NAFLD. *J. Clin. Endocrinol. Metab.* **2012**, *97*, E1088–E1098. [CrossRef] [PubMed]
137. Abdelmalek, M.F.; Lazo, M.; Horska, A.; Bonekamp, S.; Lipkin, E.W.; Balasubramanyam, A.; Bantle, J.P.; Johnson, R.J.; Diehl, A.M.; Clark, J.M.; et al. Higher dietary fructose is associated with impaired hepatic adenosine triphosphate homeostasis in obese individuals with type 2 diabetes. *Hepatology* **2012**, *56*, 952–960. [CrossRef] [PubMed]
138. Silbernagel, G.; Machann, J.; Unmuth, S.; Schick, F.; Stefan, N.; Häring, H.U.; Fritsche, A. Effects of 4-week very-high-fructose/glucose diets on insulin sensitivity, visceral fat and intrahepatic lipids: An exploratory trial. *Br. J. Nutr.* **2011**, *106*, 79–86. [CrossRef]
139. Liccardo, D.; Alisi, A.; Porta, G.; Nobili, V. Is there any link between dietary pattern and development of nonalcoholic fatty liver disease in adolescence? An expert review. *Expert Rev. Gastroenterol. Hepatol.* **2013**, *7*, 601–604. [CrossRef]
140. Gross, L.S.; Li, L.; Ford, E.S.; Liu, S. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: An ecologic assessment. *Am. J. Clin. Nutr.* **2004**, *79*, 774–779. [CrossRef]
141. Aeberli, I.; Gerber, P.A.; Hochuli, M.; Kohler, S.; Haile, S.R.; Gouni-Berthold, I.; Berthold, H.K.; Spinass, G.A.; Berneis, K. Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: A randomized controlled trial. *Am. J. Clin. Nutr.* **2011**, *94*, 479–485. [CrossRef]
142. Lê, K.A.; Bortolotti, M. Role of dietary carbohydrates and macronutrients in the pathogenesis of nonalcoholic fatty liver disease. *Curr. Opin. Clin. Nutr. Metab. Care* **2008**, *11*, 477–482. [CrossRef]
143. Nielsen, S.J.; Popkin, B.M. Changes in beverage intake between 1977 and 2001. *Am. J. Prev. Med.* **2004**, *27*, 205–210. [CrossRef]
144. EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA). Scientific opinion on dietary reference values for carbohydrates and dietary fibre. *EFSA J.* **2010**, *8*, 1462.
145. Abdelmalek, M.F.; Suzuki, A.; Guy, C.; Unalp-Arida, A.; Colvin, R.; Johnson, R.J.; Diehl, A.M.; Network, N.S.C.R. Increased fructose consumption is associated with fibrosis severity in patients with nonalcoholic fatty liver disease. *Hepatology* **2010**, *51*, 1961–1971. [CrossRef]
146. Mosca, A.; Nobili, V.; De Vito, R.; Crudele, A.; Scorletti, E.; Villani, A.; Alisi, A.; Byrne, C.D. Serum uric acid concentrations and fructose consumption are independently associated with NASH in children and adolescents. *J. Hepatol.* **2017**, *66*, 1031–1036. [CrossRef] [PubMed]
147. Nseir, W.; Nassar, F.; Assy, N. Soft drinks consumption and nonalcoholic fatty liver disease. *World J. Gastroenterol.* **2010**, *16*, 2579–2588. [CrossRef]
148. Dhingra, R.; Sullivan, L.; Jacques, P.F.; Wang, T.J.; Fox, C.S.; Meigs, J.B.; D’Agostino, R.B.; Gaziano, J.M.; Vasan, R.S. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation* **2007**, *116*, 480–488. [CrossRef] [PubMed]
149. Kirk, S.; Brehm, B.; Saelens, B.E.; Woo, J.G.; Kissel, E.; D’Alessio, D.; Bolling, C.; Daniels, S.R. Role of carbohydrate modification in weight management among obese children: A randomized clinical trial. *J. Pediatr.* **2012**, *161*, 320–327.e321. [CrossRef]
150. Spieth, L.E.; Harnish, J.D.; Lenders, C.M.; Raezer, L.B.; Pereira, M.A.; Hangen, S.J.; Ludwig, D.S. A low-glycemic index diet in the treatment of pediatric obesity. *Arch. Pediatr. Adolesc. Med.* **2000**, *154*, 947–951. [CrossRef] [PubMed]
151. Ebbeling, C.B.; Leidig, M.M.; Sinclair, K.B.; Hangen, J.P.; Ludwig, D.S. A reduced-glycemic load diet in the treatment of adolescent obesity. *Arch. Pediatr. Adolesc. Med.* **2003**, *157*, 773–779. [CrossRef] [PubMed]
152. Gupta-Smith, V. Healthy Diet. Available online: https://apps.who.int/iris/bitstream/handle/10665/42665/WHO_TRS_916.pdf?sequence=1 (accessed on 24 January 2022).
153. Rogers, D.; Campbell, R.; Catha, G.; Patterson, K.; Puccio, D. Dietary Recommendations for Healthy Children. Available online: <https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/dietary-recommendations-for-healthy-children> (accessed on 12 December 2021).

154. Matikainen, N.; Adiels, M.; Söderlund, S.; Stennabb, S.; Ahola, T.; Hakkarainen, A.; Borén, J.; Taskinen, M.R. Hepatic lipogenesis and a marker of hepatic lipid oxidation, predict postprandial responses of triglyceride-rich lipoproteins. *Obesity* **2014**, *22*, 1854–1859. [CrossRef]
155. Wang, X.; Cao, Y.; Fu, Y.; Guo, G.; Zhang, X. Liver fatty acid composition in mice with or without nonalcoholic fatty liver disease. *Lipids Health Dis.* **2011**, *10*, 234. [CrossRef]
156. Parry, S.A.; Hodson, L. Influence of dietary macronutrients on liver fat accumulation and metabolism. *J. Investig. Med.* **2017**, *65*, 1102–1115. [CrossRef] [PubMed]
157. Morandi, A.; Fornari, E.; Opri, F.; Corradi, M.; Tommasi, M.; Bonadonna, R.; Maffei, C. High-fat meal, systemic inflammation and glucose homeostasis in obese children and adolescents. *Int. J. Obes.* **2017**, *41*, 986–989. [CrossRef] [PubMed]
158. de Piano, A.; Prado, W.L.; Caranti, D.A.; Siqueira, K.O.; Stella, S.G.; Lofrano, M.; Tock, L.; Cristofalo, D.M.; Lederman, H.; Tufik, S.; et al. Metabolic and nutritional profile of obese adolescents with nonalcoholic fatty liver disease. *J. Pediatr. Gastroenterol. Nutr.* **2007**, *44*, 446–452. [CrossRef] [PubMed]
159. Dongiovanni, P.; Lanti, C.; Gatti, S.; Rametta, R.; Recalcati, S.; Maggioni, M.; Fracanzani, A.L.; Riso, P.; Cairo, G.; Fargion, S.; et al. High fat diet subverts hepatocellular iron uptake determining dysmetabolic iron overload. *PLoS ONE* **2015**, *10*, e0116855. [CrossRef]
160. Suárez, M.; Boqué, N.; Del Bas, J.M.; Mayneris-Perxachs, J.; Arola, L.; Caimari, A. Mediterranean Diet and Multi-Ingredient-Based Interventions for the Management of Non-Alcoholic Fatty Liver Disease. *Nutrients* **2017**, *9*, 1052. [CrossRef]
161. Neuschwander-Tetri, B.A. Hepatic lipotoxicity and the pathogenesis of nonalcoholic steatohepatitis: The central role of non-triglyceride fatty acid metabolites. *Hepatology* **2010**, *52*, 774–788. [CrossRef]
162. Cusi, K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: Pathophysiology and clinical implications. *Gastroenterology* **2012**, *142*, 711–725.e716. [CrossRef]
163. Bjermo, H.; Iggman, D.; Kullberg, J.; Dahlman, I.; Johansson, L.; Persson, L.; Berglund, J.; Pulkki, K.; Basu, S.; Uusitupa, M.; et al. Effects of n-6 PUFAs compared with SFAs on liver fat, lipoproteins, and inflammation in abdominal obesity: A randomized controlled trial. *Am. J. Clin. Nutr.* **2012**, *95*, 1003–1012. [CrossRef]
164. Vessby, B.; Uusitupa, M.; Hermansen, K.; Riccardi, G.; Rivellese, A.A.; Tapsell, L.C.; Näslén, C.; Berglund, L.; Louheranta, A.; Rasmussen, B.M.; et al. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU Study. *Diabetologia* **2001**, *44*, 312–319. [CrossRef]
165. Lapointe, A.; Couillard, C.; Lemieux, S. Effects of dietary factors on oxidation of low-density lipoprotein particles. *J. Nutr. Biochem.* **2006**, *17*, 645–658. [CrossRef] [PubMed]
166. Williams, C.M. Beneficial nutritional properties of olive oil: Implications for postprandial lipoproteins and factor VII. *Nutr. Metab. Cardiovasc. Dis.* **2001**, *11*, 51–56. [PubMed]
167. Rajaram, S.; Burke, K.; Connell, B.; Myint, T.; Sabaté, J. A monounsaturated fatty acid-rich pecan-enriched diet favorably alters the serum lipid profile of healthy men and women. *J. Nutr.* **2001**, *131*, 2275–2279. [CrossRef]
168. Kris-Etherton, P.M.; Pearson, T.A.; Wan, Y.; Hargrove, R.L.; Moriarty, K.; Fishell, V.; Etherton, T.D. High-monounsaturated fatty acid diets lower both plasma cholesterol and triacylglycerol concentrations. *Am. J. Clin. Nutr.* **1999**, *70*, 1009–1015. [CrossRef]
169. Julius, U. Fat modification in the diabetes diet. *Exp. Clin. Endocrinol. Diabetes* **2003**, *111*, 60–65. [CrossRef]
170. Meeta Agarwal, M.A. MUFA and PUFA Foods. Available online: <https://www.medindia.net/patients/lifestyleandwellness/mufa-and-pufa-foods.htm> (accessed on 2 February 2022).
171. Reiner, Z.; Catapano, A.L.; De Backer, G.; Graham, I.; Taskinen, M.R.; Wiklund, O.; Agewall, S.; Alegria, E.; Chapman, M.J.; Durrington, P.; et al. ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur. Heart J.* **2011**, *32*, 1769–1818. [CrossRef] [PubMed]
172. Jump, D.B.; Tripathy, S.; Depner, C.M. Fatty acid-regulated transcription factors in the liver. *Annu. Rev. Nutr.* **2013**, *33*, 249–269. [CrossRef]
173. Li, T.; Chiang, J.Y. Bile acid signaling in metabolic disease and drug therapy. *Pharmacol. Rev.* **2014**, *66*, 948–983. [CrossRef]
174. Campos, R.M.; de Piano, A.; da Silva, P.L.; Carnier, J.; Sanches, P.L.; Corgosinho, F.C.; Masquio, D.C.; Lazaretti-Castro, M.; Oyama, L.M.; Nascimento, C.M.; 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. [CrossRef]
175. Sekkarie, A.; Welsh, J.A.; Vos, M.B. Carbohydrates and diet patterns in nonalcoholic fatty liver disease in children and adolescents. *Curr. Opin. Clin. Nutr. Metab. Care* **2018**, *21*, 283–288. [CrossRef]
176. Ramon-Krauel, M.; Salsberg, S.L.; Ebbeling, C.B.; Voss, S.D.; Mulkern, R.V.; Apura, M.M.; Cooke, E.A.; Sarao, K.; Jonas, M.M.; Ludwig, D.S. A low-glycemic-load versus low-fat diet in the treatment of fatty liver in obese children. *Child. Obes.* **2013**, *9*, 252–260. [CrossRef]
177. Nobili, V.; Bedogni, G.; Alisi, A.; Pietrobattista, A.; Risé, P.; Galli, C.; Agostoni, C. 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. [CrossRef]
178. Puri, P.; Baillie, R.A.; Wiest, M.M.; Mirshahi, F.; Choudhury, J.; Cheung, O.; Sargeant, C.; Contos, M.J.; Sanyal, A.J. A lipidomic analysis of nonalcoholic fatty liver disease. *Hepatology* **2007**, *46*, 1081–1090. [CrossRef]

179. Cardel, M.; Lemas, D.J.; Jackson, K.H.; Friedman, J.E.; Fernández, J.R. Higher Intake of PUFAs Is Associated with Lower Total and Visceral Adiposity and Higher Lean Mass in a Racially Diverse Sample of Children. *J. Nutr.* **2015**, *145*, 2146–2152. [CrossRef]
180. Chakravarthy, M.V.; Waddell, T.; Banerjee, R.; Guess, N. Nutrition and Nonalcoholic Fatty Liver Disease: Current Perspectives. *Gastroenterol. Clin. N. Am.* **2020**, *49*, 63–94. [CrossRef] [PubMed]
181. Risérus, U. Fatty acids and insulin sensitivity. *Curr. Opin. Clin. Nutr. Metab. Care* **2008**, *11*, 100–105. [CrossRef]
182. Kaitosaari, T.; Rönnemaa, T.; Viikari, J.; Raitakari, O.; Arffman, M.; Marniemi, J.; Kallio, K.; Pakkala, K.; Jokinen, E.; Simell, O. Low-saturated fat dietary counseling starting in infancy improves insulin sensitivity in 9-year-old healthy children: The Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) study. *Diabetes Care* **2006**, *29*, 781–785. [CrossRef]
183. Papandreou, D.; Rousso, I.; Malindretos, P.; Makedou, A.; Moudiou, T.; Pidonia, I.; Pantoleon, A.; Economou, I.; Mavromichalis, I. Are saturated fatty acids and insulin resistance associated with fatty liver in obese children? *Clin. Nutr.* **2008**, *27*, 233–240. [CrossRef]
184. Papandreou, D.; Karabouta, Z.; Pantoleon, A.; Rousso, I. Investigation of anthropometric, biochemical and dietary parameters of obese children with and without non-alcoholic fatty liver disease. *Appetite* **2012**, *59*, 939–944. [CrossRef] [PubMed]
185. Quirós-Tejeira, R.E.; Rivera, C.A.; Ziba, T.T.; Mehta, N.; Smith, C.W.; Butte, N.F. Risk for nonalcoholic fatty liver disease in Hispanic youth with BMI > or =95th percentile. *J. Pediatr. Gastroenterol. Nutr.* **2007**, *44*, 228–236. [CrossRef] [PubMed]
186. Kargulewicz, A.; Stankowiak-Kulpa, H.; Grzymisławski, M. Dietary recommendations for patients with nonalcoholic fatty liver disease. *Prz. Gastroenterol.* **2014**, *9*, 18–23. [CrossRef] [PubMed]
187. Leclercq, I.A.; Horsmans, Y. Nonalcoholic fatty liver disease: The potential role of nutritional management. *Curr. Opin. Clin. Nutr. Metab. Care* **2008**, *11*, 766–773. [CrossRef] [PubMed]
188. Zelber-Sagi, S.; Nitzan-Kaluski, D.; Goldsmith, R.; Webb, M.; Blendis, L.; Halpern, Z.; Oren, R. Long term nutritional intake and the risk for non-alcoholic fatty liver disease (NAFLD): A population based study. *J. Hepatol.* **2007**, *47*, 711–717. [CrossRef]
189. Wehmeyer, M.H.; Zyriax, B.C.; Jagemann, B.; Roth, E.; Windler, E.; Schulze Zur Wiesch, J.; Lohse, A.W.; Kluwe, J. Nonalcoholic fatty liver disease is associated with excessive calorie intake rather than a distinctive dietary pattern. *Medicine* **2016**, *95*, e3887. [CrossRef]
190. Cortez-Pinto, H.; Jesus, L.; Barros, H.; Lopes, C.; Moura, M.C.; Camilo, M.E. How different is the dietary pattern in non-alcoholic steatohepatitis patients? *Clin. Nutr.* **2006**, *25*, 816–823. [CrossRef]
191. Volynets, V.; Küper, M.A.; Strahl, S.; Maier, I.B.; Spruss, A.; Wagnerberger, S.; Königsrainer, A.; Bischoff, S.C.; Bergheim, I. Nutrition, intestinal permeability, and blood ethanol levels are altered in patients with nonalcoholic fatty liver disease (NAFLD). *Dig. Dis. Sci.* **2012**, *57*, 1932–1941. [CrossRef] [PubMed]
192. Cheng, Y.; Zhang, K.; Chen, Y.; Li, Y.; Fu, K.; Feng, R. Associations between Dietary Nutrient Intakes and Hepatic Lipid Contents in NAFLD Patients Quantified by ¹H-MRS and Dual-Echo MRI. *Nutrients* **2016**, *8*, 527. [CrossRef]
193. Markova, M.; Pivovarova, O.; Hornemann, S.; Sucher, S.; Frahnow, T.; Wegner, K.; Machann, J.; Petzke, K.J.; Hierholzer, J.; Lichtinghagen, R.; et al. Isocaloric Diets High in Animal or Plant Protein Reduce Liver Fat and Inflammation in Individuals With Type 2 Diabetes. *Gastroenterology* **2017**, *152*, 571–585.e578. [CrossRef]
194. Bortolotti, M.; Kreis, R.; Debar, C.; Cariou, B.; Faeh, D.; Chetiveaux, M.; Ith, M.; Vermathen, P.; Stefanoni, N.; Lê, K.A.; et al. High protein intake reduces intrahepatocellular lipid deposition in humans. *Am. J. Clin. Nutr.* **2009**, *90*, 1002–1010. [CrossRef]
195. De Vito, R.; Alisi, A.; Masotti, A.; Ceccarelli, S.; Panera, N.; Citti, A.; Salata, M.; Valenti, L.; Feldstein, A.E.; Nobili, V. Markers of activated inflammatory cells correlate with severity of liver damage in children with nonalcoholic fatty liver disease. *Int. J. Mol. Med.* **2012**, *30*, 49–56. [CrossRef]
196. Arciero, P.J.; Gentile, C.L.; Pressman, R.; Everett, M.; Ormsbee, M.J.; Martin, J.; Santamore, J.; Gorman, L.; Fehling, P.C.; Vukovich, M.D.; et al. Moderate protein intake improves total and regional body composition and insulin sensitivity in overweight adults. *Metabolism* **2008**, *57*, 757–765. [CrossRef] [PubMed]
197. Meghelli-Bouchenak, M.; Belleville, J.; Boquillon, M. Hepatic steatosis and serum very low density lipoproteins during two types of protein malnutrition followed by balanced refeeding. *Nutrition* **1989**, *5*, 321–329. [PubMed]
198. Ampong, I.; Watkins, A.; Gutierrez-Merino, J.; Ikwuobe, J.; Griffiths, H.R. Dietary protein insufficiency: An important consideration in fatty liver disease? *Br. J. Nutr.* **2020**, *123*, 601–609. [CrossRef]
199. Agius, L. High-carbohydrate diets induce hepatic insulin resistance to protect the liver from substrate overload. *Biochem. Pharmacol.* **2013**, *85*, 306–312. [CrossRef] [PubMed]
200. Nazarenko, L.I.; Petrova, I.N.; Raïkhel'son, K.L.; Baranovskii, A.I. Nutrition mistakes in patients with nonalcoholic fatty liver disease and the ways of correction. *Eksp. Klin. Gastroenterol.* **2012**, 19–24. Available online: <https://pubmed.ncbi.nlm.nih.gov/22808787/> (accessed on 28 March 2022).
201. Yang, H.Y.; Tzeng, Y.H.; Chai, C.Y.; Hsieh, A.T.; Chen, J.R.; Chang, L.S.; Yang, S.S. Soy protein retards the progression of non-alcoholic steatohepatitis via improvement of insulin resistance and steatosis. *Nutrition* **2011**, *27*, 943–948. [CrossRef]
202. Vajro, P.; Mandato, C.; Franzese, A.; Ciccimarra, E.; Lucariello, S.; Savoia, M.; Capuano, G.; Migliaro, F. Vitamin E treatment in pediatric obesity-related liver disease: A randomized study. *J. Pediatr. Gastroenterol. Nutr.* **2004**, *38*, 48–55. [CrossRef]
203. Nobili, V.; Manco, M.; Devito, R.; Di Ciommo, V.; Comparcola, D.; Sartorelli, M.R.; Piemonte, F.; Marcellini, M.; Angulo, P. Lifestyle intervention and antioxidant therapy in children with nonalcoholic fatty liver disease: A randomized, controlled trial. *Hepatology* **2008**, *48*, 119–128. [CrossRef]

204. Koot, B.G.; van der Baan-Slootweg, O.H.; Tamminga-Smeulders, C.L.; Rijcken, T.H.; Korevaar, J.C.; van Aalderen, W.M.; Jansen, P.L.; Benninga, M.A. Lifestyle intervention for non-alcoholic fatty liver disease: Prospective cohort study of its efficacy and factors related to improvement. *Arch. Dis. Child.* **2011**, *96*, 669–674. [[CrossRef](#)]
205. Promrat, K.; Kleiner, D.E.; Niemeier, H.M.; Jackvony, E.; Kearns, M.; Wands, J.R.; Fava, J.L.; Wing, R.R. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology* **2010**, *51*, 121–129. [[CrossRef](#)]
206. Reinehr, T.; Schmidt, C.; Toschke, A.M.; Andler, W. Lifestyle intervention in obese children with non-alcoholic fatty liver disease: 2-year follow-up study. *Arch. Dis. Child.* **2009**, *94*, 437–442. [[CrossRef](#)]
207. 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. [[CrossRef](#)]
208. Grønbaek, H.; Lange, A.; Birkebæk, N.H.; Holland-Fischer, P.; Solvig, J.; Hørlyck, A.; Kristensen, K.; Rittig, S.; Vilstrup, H. 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. [[CrossRef](#)]
209. Vos, M.B.; Weber, M.B.; Welsh, J.; Khatoun, F.; Jones, D.P.; Whittington, P.F.; McClain, C.J. Fructose and oxidized low-density lipoprotein in pediatric nonalcoholic fatty liver disease: A pilot study. *Arch. Pediatr. Adolesc. Med.* **2009**, *163*, 674–675. [[CrossRef](#)]
210. Mann, J.P.; Valenti, L.; Scorletti, E.; Byrne, C.D.; Nobili, V. Nonalcoholic Fatty Liver Disease in Children. *Semin. Liver Dis.* **2018**, *38*, 1–13. [[CrossRef](#)]
211. Boyraz, M.; Pirgon, Ö.; Dündar, B.; Çekmez, F.; Hatipoğlu, N. Long-Term Treatment with n-3 Polyunsaturated Fatty Acids as a Monotherapy in Children with Nonalcoholic Fatty Liver Disease. *J. Clin. Res. Pediatr. Endocrinol.* **2015**, *7*, 121–127. [[CrossRef](#)]
212. Clemens, R.A.; Jones, J.M.; Kern, M.; Lee, S.Y.; Mayhew, E.J.; Slavina, J.L.; Zivanovic, S. Functionality of Sugars in Foods and Health. *Compr. Rev. Food Sci. Food Saf.* **2016**, *15*, 433–470. [[CrossRef](#)]
213. Aller, E.E.; Abete, I.; Astrup, A.; Martinez, J.A.; van Baak, M.A. Starches, sugars and obesity. *Nutrients* **2011**, *3*, 341–369. [[CrossRef](#)]
214. Augustin, L.S.A.; Kendall, C.W.C.; Jenkins, D.J.A.; Willett, W.C.; Astrup, A.; Barclay, A.W.; Björck, I.; Brand-Miller, J.C.; Brighenti, F.; Buyken, A.E.; et al. Glycemic index, glycemic load and glycemic response: An International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). *Nutr. Metab. Cardiovasc. Dis.* **2015**, *25*, 795–815. [[CrossRef](#)]
215. Haufe, S.; Engeli, S.; Kast, P.; Böhnke, J.; Utz, W.; Haas, V.; Hermsdorf, M.; Mähler, A.; Wiesner, S.; Birkenfeld, A.L.; et al. Randomized comparison of reduced fat and reduced carbohydrate hypocaloric diets on intrahepatic fat in overweight and obese human subjects. *Hepatology* **2011**, *53*, 1504–1514. [[CrossRef](#)] [[PubMed](#)]
216. Anania, C.; Perla, F.M.; Olivero, F.; Pacifico, L.; Chiesa, C. Mediterranean diet and nonalcoholic fatty liver disease. *World J. Gastroenterol.* **2018**, *24*, 2083–2094. [[CrossRef](#)]
217. Tosti, V.; Bertozzi, B.; Fontana, L. Health Benefits of the Mediterranean Diet: Metabolic and Molecular Mechanisms. *J. Gerontol. A Biol. Sci. Med. Sci.* **2018**, *73*, 318–326. [[CrossRef](#)] [[PubMed](#)]
218. Trichopoulou, A.; Martínez-González, M.A.; Tong, T.Y.; Forouhi, N.G.; Khandelwal, S.; Prabhakaran, D.; Mozaffarian, D.; de Lorgeril, M. Definitions and potential health benefits of the Mediterranean diet: Views from experts around the world. *BMC Med.* **2014**, *12*, 112. [[CrossRef](#)]
219. Abenavoli, L.; Milic, N.; Peta, V.; Alfieri, F.; De Lorenzo, A.; Bellentani, S. Alimentary regimen in non-alcoholic fatty liver disease: Mediterranean diet. *World J. Gastroenterol.* **2014**, *20*, 16831–16840. [[CrossRef](#)] [[PubMed](#)]
220. Abenavoli, L.; Greco, M.; Nazionale, I.; Peta, V.; Milic, N.; Accattato, F.; Foti, D.; Gulletta, E.; Luzzza, F. Effects of Mediterranean diet supplemented with silybin-vitamin E-phospholipid complex in overweight patients with non-alcoholic fatty liver disease. *Expert Rev. Gastroenterol. Hepatol.* **2015**, *9*, 519–527. [[CrossRef](#)]
221. Yki-Järvinen, H. Nutritional Modulation of Non-Alcoholic Fatty Liver Disease and Insulin Resistance. *Nutrients* **2015**, *7*, 9127–9138. [[CrossRef](#)] [[PubMed](#)]
222. Kastorini, C.M.; Milionis, H.J.; Esposito, K.; Giugliano, D.; Goudevenos, J.A.; Panagiotakos, D.B. The effect of Mediterranean diet on metabolic syndrome and its components: A meta-analysis of 50 studies and 534,906 individuals. *J. Am. Coll. Cardiol.* **2011**, *57*, 1299–1313. [[CrossRef](#)]
223. Esposito, K.; Kastorini, C.M.; Panagiotakos, D.B.; Giugliano, D. Mediterranean diet and metabolic syndrome: An updated systematic review. *Rev. Endocr. Metab. Disord.* **2013**, *14*, 255–263. [[CrossRef](#)]
224. Cakir, M.; Akbulut, U.E.; Okten, A. Association between Adherence to the Mediterranean Diet and Presence of Nonalcoholic Fatty Liver Disease in Children. *Child. Obes.* **2016**, *12*, 279–285. [[CrossRef](#)]
225. Kosinski, C.; Jornayvaz, F.R. Effects of Ketogenic Diets on Cardiovascular Risk Factors: Evidence from Animal and Human Studies. *Nutrients* **2017**, *9*, 517. [[CrossRef](#)]
226. Ilan, Y. Leaky gut and the liver: A role for bacterial translocation in nonalcoholic steatohepatitis. *World J. Gastroenterol.* **2012**, *18*, 2609–2618. [[CrossRef](#)]
227. Song, Y.; Manson, J.E.; Buring, J.E.; Liu, S. A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: The women’s health study. *Diabetes Care* **2004**, *27*, 2108–2115. [[CrossRef](#)] [[PubMed](#)]
228. Han, J.M.; Jo, A.N.; Lee, S.M.; Bae, H.S.; Jun, D.W.; Cho, Y.K.; Suk, K.T.; Yoon, J.H.; Ahn, S.B.; Cho, Y.J.; et al. Associations between intakes of individual nutrients or whole food groups and non-alcoholic fatty liver disease among Korean adults. *J. Gastroenterol. Hepatol.* **2014**, *29*, 1265–1272. [[CrossRef](#)] [[PubMed](#)]

229. Shi, L.; Liu, Z.W.; Li, Y.; Gong, C.; Zhang, H.; Song, L.J.; Huang, C.Y.; Li, M. The prevalence of nonalcoholic fatty liver disease and its association with lifestyle/dietary habits among university faculty and staff in Chengdu. *Biomed. Environ. Sci.* **2012**, *25*, 383–391. [[CrossRef](#)] [[PubMed](#)]
230. Collison, K.S.; Maqbool, Z.; Saleh, S.M.; Inglis, A.; Makhoul, N.J.; Bakheet, R.; Al-Johi, M.; Al-Rabiah, R.; Zaidi, M.Z.; Al-Mohanna, F.A. Effect of dietary monosodium glutamate on trans fat-induced nonalcoholic fatty liver disease. *J. Lipid Res.* **2009**, *50*, 1521–1537. [[CrossRef](#)] [[PubMed](#)]
231. Hardy, L.L.; Bell, J.; Bauman, A.; Mirshahi, S. Association between adolescents' consumption of total and different types of sugar-sweetened beverages with oral health impacts and weight status. *Aust. N. Z. J. Public Health* **2018**, *42*, 22–26. [[CrossRef](#)]
232. Hooper, L.; Abdelhamid, A.; Bunn, D.; Brown, T.; Summerbell, C.D.; Skeaff, C.M. Effects of total fat intake on body weight. *Cochrane Database Syst. Rev.* **2015**, CD011834. [[CrossRef](#)]
233. You, J.; Choo, J. Adolescent Overweight and Obesity: Links to Socioeconomic Status and Fruit and Vegetable Intakes. *Int. J. Environ. Res. Public Health* **2016**, *13*, 307. [[CrossRef](#)]
234. Danford, C.A.; Schultz, C.; Marvicsin, D. Parental roles in the development of obesity in children: Challenges and opportunities. *Dovepress* **2014**, *2015*, 39–46. [[CrossRef](#)]
235. Gregory, J.W. Prevention of Obesity and Metabolic Syndrome in Children. *Front. Endocrinol.* **2019**, *10*, 669. [[CrossRef](#)] [[PubMed](#)]
236. Marcellini, F.; Giuli, C.; Papa, R.; Tirabassi, G.; Faloia, E.; Boscaro, M.; Polito, A.; Ciarapica, D.; Zaccaria, M.; Mocchegiani, E. Obesity and body mass index (BMI) in relation to life-style and psycho-social aspects. *Arch. Gerontol. Geriatr.* **2009**, *49* (Suppl. 1), 195–206. [[CrossRef](#)] [[PubMed](#)]
237. Sedibe, M.H.; Pisa, P.T.; Feeley, A.B.; Pedro, T.M.; Kahn, K.; Norris, S.A. Dietary Habits and Eating Practices and Their Association with Overweight and Obesity in Rural and Urban Black South African Adolescents. *Nutrients* **2018**, *10*, 145. [[CrossRef](#)] [[PubMed](#)]
238. Allegri, C.; Turconi, G.; Cena, H. Dietary attitudes and diseases of comfort. *Eat. Weight Disord.* **2011**, *16*, e226–e235. [[CrossRef](#)] [[PubMed](#)]
239. De Giuseppe, R.; Di Napoli, I.; Porri, D.; Cena, H. Pediatric Obesity and Eating Disorders Symptoms: The Role of the Multidisciplinary Treatment. A Systematic Review. *Front. Pediatr.* **2019**, *7*, 123. [[CrossRef](#)]
240. Temple, J.L.; Cordero, P.; Li, J.; Nguyen, V.; Oben, J.A. A Guide to Non-Alcoholic Fatty Liver Disease in Childhood and Adolescence. *Int. J. Mol. Sci.* **2016**, *17*, 947. [[CrossRef](#)]
241. Goldner, D.; Lavine, J.E. Nonalcoholic Fatty Liver Disease in Children: Unique Considerations and Challenges. *Gastroenterology* **2020**, *158*, 1967–1983.e1961. [[CrossRef](#)]
242. Zhao, L.; Zhang, F.; Ding, X.; Wu, G.; Lam, Y.Y.; Wang, X.; Fu, H.; Xue, X.; Lu, C.; Ma, J.; et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science* **2018**, *359*, 1151–1156. [[CrossRef](#)]
243. Alisi, A.; Nobili, V. Non-alcoholic fatty liver disease in children now: Lifestyle changes and pharmacologic treatments. *Nutrition* **2012**, *28*, 722–726. [[CrossRef](#)]
244. Huang, M.A.; Greenon, J.K.; Chao, C.; Anderson, L.; Peterman, D.; Jacobson, J.; Emick, D.; Lok, A.S.; Conjeevaram, H.S. One-year intense nutritional counseling results in histological improvement in patients with non-alcoholic steatohepatitis: A pilot study. *Am. J. Gastroenterol.* **2005**, *100*, 1072–1081. [[CrossRef](#)]
245. Chalasani, N.; Younossi, Z.; Lavine, J.E.; Diehl, A.M.; Brunt, E.M.; Cusi, K.; Charlton, M.; Sanyal, A.J. 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. [[CrossRef](#)] [[PubMed](#)]
246. Della Corte, C.; Vajro, P.; Socha, P.; Nobili, V. Pediatric non-alcoholic fatty liver disease: Recent advances. *Clin. Res. Hepatol. Gastroenterol.* **2014**, *38*, 419–422. [[CrossRef](#)]
247. Barlow, S.E.; Dietz, W.H. Management of child and adolescent obesity: Summary and recommendations based on reports from pediatricians, pediatric nurse practitioners, and registered dietitians. *Pediatrics* **2002**, *110*, 236–238. [[CrossRef](#)] [[PubMed](#)]
248. Goodpaster, B.H.; Sparks, L.M. Metabolic Flexibility in Health and Disease. *Cell Metab.* **2017**, *25*, 1027–1036. [[CrossRef](#)]
249. Sofi, F.; Macchi, C.; Abbate, R.; Gensini, G.F.; Casini, A. Mediterranean diet and health. *Biofactors* **2013**, *39*, 335–342. [[CrossRef](#)]
250. Collison, K.S.; Saleh, S.M.; Bakheet, R.H.; Al-Rabiah, R.K.; Inglis, A.L.; Makhoul, N.J.; Maqbool, Z.M.; Zaidi, M.Z.; Al-Johi, M.A.; Al-Mohanna, F.A. Diabetes of the liver: The link between nonalcoholic fatty liver disease and HFCS-55. *Obesity* **2009**, *17*, 2003–2013. [[CrossRef](#)] [[PubMed](#)]
251. Wang, D.; Wei, Y.; Pagliassotti, M.J. Saturated fatty acids promote endoplasmic reticulum stress and liver injury in rats with hepatic steatosis. *Endocrinology* **2006**, *147*, 943–951. [[CrossRef](#)]
252. Lopez-Garcia, E.; Schulze, M.B.; Meigs, J.B.; Manson, J.E.; Rifai, N.; Stampfer, M.J.; Willett, W.C.; Hu, F.B. Consumption of trans fatty acids is related to plasma biomarkers of inflammation and endothelial dysfunction. *J. Nutr.* **2005**, *135*, 562–566. [[CrossRef](#)]
253. Anderson, J.W.; Randles, K.M.; Kendall, C.W.; Jenkins, D.J. Carbohydrate and fiber recommendations for individuals with diabetes: A quantitative assessment and meta-analysis of the evidence. *J. Am. Coll. Nutr.* **2004**, *23*, 5–17. [[CrossRef](#)]
254. Brighenti, F.; Benini, L.; Del Rio, D.; Casiraghi, C.; Pellegrini, N.; Scazzina, F.; Jenkins, D.J.; Vantini, I. Colonic fermentation of indigestible carbohydrates contributes to the second-meal effect. *Am. J. Clin. Nutr.* **2006**, *83*, 817–822. [[CrossRef](#)]
255. Bozzetto, L.; Prinster, A.; Annuzzi, G.; Costagliola, L.; Mangione, A.; Vitelli, A.; Mazzarella, R.; Longobardo, M.; Mancini, M.; Vigorito, C.; et al. Liver fat is reduced by an isoenergetic MUFA diet in a controlled randomized study in type 2 diabetic patients. *Diabetes Care* **2012**, *35*, 1429–1435. [[CrossRef](#)] [[PubMed](#)]

256. Nobili, V.; Carpino, G.; Alisi, A.; De Vito, R.; Franchitto, A.; Alpini, G.; Onori, P.; Gaudio, E. Role of docosahexaenoic acid treatment in improving liver histology in pediatric nonalcoholic fatty liver disease. *PLoS ONE* **2014**, *9*, e88005. [[CrossRef](#)] [[PubMed](#)]
257. Nobili, V.; Socha, P. Pediatric Nonalcoholic Fatty Liver Disease: Current Thinking. *J. Pediatr. Gastroenterol. Nutr.* **2018**, *66*, 188–192. [[CrossRef](#)]
258. Furthner, D.; Weghuber, D.; Dalus, C.; Lukas, A.; Stundner-Ladenhauf, H.N.; Mangge, H.; Pixner, T. Nonalcoholic Fatty Liver Disease in Children with Obesity: Narrative Review and Research Gaps. *Horm. Res. Paediatr.* **2021**, *94*, 239–248. [[CrossRef](#)]
259. Barlow, S.E.; Committee, E. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: Summary report. *Pediatrics* **2007**, *120* (Suppl. 4), S164–S192. [[CrossRef](#)] [[PubMed](#)]
260. Paoletta, G.; Vajro, P. Childhood Obesity, Breastfeeding, Intestinal Microbiota, and Early Exposure to Antibiotics: What Is the Link? *JAMA Pediatr.* **2016**, *170*, 735–737. [[CrossRef](#)] [[PubMed](#)]
261. Poeta, M.; Di Salvio, D.; Torsiello, N.; Massa, G.; Guercio Nuzio, S.; Savastano, R.; Alfano, G.; Pierri, L.; Tripodi, M.; Siano, M.; et al. Obesity prevention project in preschoolage: The 3P-Project effectiveness in short- and medium-term. In Proceedings of the 49th ESPGHAN Meeting, Athens, Greece, 25–28 May 2016.