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Olesya Horlenko, Olga Pushkarenko

Niealkoholowa stłuszczeniowa choroba wątroby u dzieci i młodzieży: metaanaliza

Non-alcoholic fatty liver disease in children and adolescents: a meta-analysis

Department of Paediatrics, Medicine Faculty, Uzhhorod National University, Uzhhorod, Ukraine
Adres do korespondencji: Olesya Horlenko, Department of Paediatrics with Infectious Diseases, Medical Faculty, Uzhhorod National University, 88000, Ukraine, Zakarpattya, Uzhhorod, Rakoci str. 3, tel.: +380505269658

ORCID iDs
1. Olesya Horlenko https://orcid.org/0000-0002-2210-5503
2. Olga Pushkarenko https://orcid.org/0000-0002-7143-029X

Streszczenie

Cel: Niealkoholowa stłuszczeniowa choroba wątroby jest najczęstszą przewlekłą chorobą wątroby występującą u dzieci i młodzieży. Wykazuje związek z szeregiem czynników ryzyka, m.in. otyłością, zespołem metabolicznym, siedzącym trybem życia itp. Celem niniejszej pracy jest przegląd najnowszych danych dotyczących częstości występowania i możliwości leczenia niealkoholowej stłuszczeniowej choroby wątroby u dzieci i młodzieży. **Materiały i metody:** Na potrzeby metaanalizy autorki przeprowadziły kompleksowy systematyczny przegląd piśmiennictwa, m.in. przeszukując bazę danych PubMed pod kątem badań powiązanych tematycznie z metaanalizą, opublikowanych w okresie do września 2021 roku. Opracowano dokładny proces selekcji, aby wybrać badania kwalifikujące się do dalszej analizy. **Wyniki:** Badania dotyczące chorobowości uwzględnione w metaanalizie obejmowały łącznie 27 241 dzieci i nastolatków. Zbiorcza średnia częstość występowania niealkoholowej stłuszczeniowej choroby wątroby wyniosła 22,64%. Stwierdzono znaczny stopień niejednorodności (I^2 = 43%) oraz znamienną różnicę (p < 0,00001) w częstości występowania choroby wśród dzieci i młodzieży w poszczególnych badaniach. Wyniki wykazały również większą częstość występowania u młodzieży niż u dzieci. Najczęściej stosowaną metodą szacowania chorobowości w badaniach włączonych do metaanalizy było stężenie aminotransferazy alaninowej. W poszczególnych badaniach przyjęto różne strategie leczenia niealkoholowej stłuszczeniowej choroby wątroby u dzieci/młodzieży, a jako miary wyników leczenia wykorzystywano zmiany wskaźnika masy ciała oraz stężenia aminotransferaz (aminotransferazy alaninowej/asparaginianowej). Wśród badań uwzględnionych w metaanalizie odnotowano statystycznie nieznamienną różnicę w wartościach wskaźnika masy ciała (p = 0,02). Z kolei zbiorczy efekt aminotransferazy alaninowej szacowany przy pomocy modelu losowego wyniósł 13,52 (7,28, 19,76). Po leczeniu obserwowano znamienną różnicę w wartościach zbiorczych stężeń aminotransferazy alaninowej (p < 0,00001). **Wnioski:** Niealkoholowa stłuszczeniowa choroba wątroby jest często odnotowywana wśród dzieci i młodzieży. Zmiana stylu życia i inne dostępne metody leczenia mogą w istotny sposób przyczyniać się do zmniejszenia częstości występowania tego schorzenia w tej populacji.

Słowa kluczowe: niealkoholowa stłuszczeniowa choroba wątroby, otyłość, zespół metaboliczny, dzieci, młodzież, metaanaliza

Abstract

Aim: Non-alcoholic fatty liver disease is the most common chronic liver disease in children and adolescents. It is associated with various risk factors including obesity, metabolic syndrome, sedentary lifestyle, etc. The present study was aimed to give an overview of the latest data on the prevalence and treatment options for non-alcoholic fatty liver disease in children and adolescents. **Materials and methods:** For the purpose of this meta-analysis, we conducted a comprehensive systematic literature review including a PubMed database search for related studies until September 2021. A thorough selection process was then adopted to select eligible studies for further analysis. **Results:** The selected prevalence studies in this meta-analysis included 27,241 children and adolescents, with a pooled mean prevalence of 22.64%. There was a marked heterogeneity (I^2 = 43%) and a significant difference (p < 0.00001) in the prevalence of non-alcoholic fatty liver disease among children and adolescents across the studies. The results also showed a greater prevalence of non-alcoholic fatty liver disease in adolescents as compared to children. The most widely used method for the estimation of prevalence among selected studies was alanine transaminase levels. However, various treatment strategies were adopted in different studies for non-alcoholic fatty liver disease in children/adolescents, and changes in body mass index and aminotransferase levels (alanine transaminase/aspartate transaminase) were used as outcome measures after treatment. Overall, there was a non-significant difference in body mass index values (p = 0.02) among the selected studies. However, the combined effect of alanine transaminase by using a random model was 13.52 (7.28, 19.76), and a significant difference in pooled alanine transaminase values (p < 0.00001) was observed

after treatment. **Conclusion:** There is a high prevalence of non-alcoholic fatty liver disease among children and adolescents. However, lifestyle interventions and other treatment methods have a significant impact on reducing the occurrence of the disease in children and adolescents.

Keywords: non-alcoholic fatty liver disease, obesity, metabolic syndrome, children, adolescents, meta-analysis

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), characterised by fat accumulation in more than 5% of hepatocytes, is the most prevalent chronic liver disease in children and adolescents, and it is on the rise with rising rates of obesity[1]. The incidence of NAFLD is rapidly increasing, with more than 30% of European children being obese[2]. Obesity affects 16.9% of children aged 2 to 19 years in the United States as well[3]. NAFLD is a multisystem condition that impairs both the liver and extrahepatic organs, and it has a long-term impact on health that lasts into adulthood, resulting in considerable morbidity and mortality[4,5]. As showed in Fig. 1, NAFLD in children and adolescents is linked to a number of risk factors, including maternal overnutrition, sedentary lifestyle, genetic variation, gestational diabetes mellitus, metabolic syndrome, and others[6].

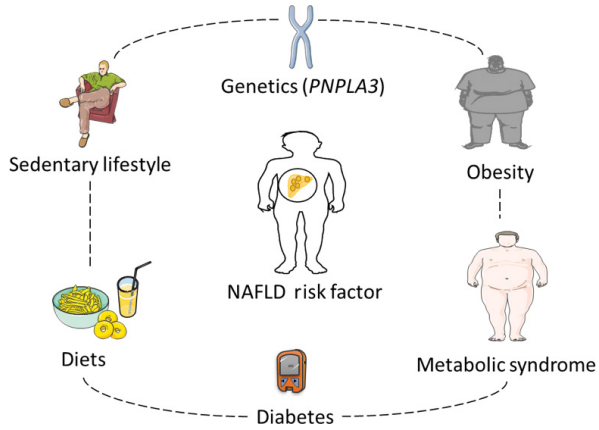
Simple hepatic steatosis and non-alcoholic steatohepatitis (NASH), the latter of which is defined by hepatocellular steatosis and inflammation with or without fibrosis, are two histological subtypes of NAFLD[7]. The biochemical profile (aminotransferases), characteristic imaging findings, and negative tests for other liver diseases can all be used in the diagnostic work-up for NAFLD. However, the gold standard for diagnosing NAFLD is biopsy, since it can demonstrate steatosis, inflammation, or fibrosis[8]. Indirect techniques of diagnosis have also been employed, as biopsy has significant limitations[1]. In a person who does not drink alcohol excessively, the diagnostic criteria include 5% of hepatocytes with large vesicular steatosis and no indication of viral, autoimmune, genetic metabolic, or drug-induced liver diseases[4]. A combination of prenatal and postnatal genetic and epigenetic factors, as well as a substantial psychosocial component, are known to induce NAFLD[6,9]. Multiple mechanisms are required to convert excess dietary carbohydrates and fatty acids into free fatty acids (FFA). The liver transforms these fatty acids into triglycerides, which are then exported into the bloodstream as very-low-density lipoprotein (VLDL). As seen in Fig. 2, an excess of carbohydrate and fatty acid substrates, as well as defective fatty acid disposal pathways, result in the formation of lipotoxic species that cause hepatocellular damage. Some studies also report on the potential role of gut microbiota in NAFLD patients with obesity and type 2 diabetes mellitus. It has also been observed that alterations in gut microbiota signatures influence hepatic lipid and carbohydrate metabolism, as well as affecting the balance between anti-inflammatory and pro-inflammatory effectors in the liver, thus impacting NAFLD and its progression to NASH[12–14].

Much is already known about NAFLD in children and adolescents, and new information is released on a regular basis. The purpose of this meta-analysis is to provide practicing physicians with concise up-to-date information about NAFLD in children and adolescents, along with brief information on recent breakthroughs and methods for the prevention and therapy of paediatric NAFLD.

MATERIALS AND METHODS

Study selection and data extraction

In September 2021, we conducted a search for this systematic review/meta-analysis including the most recent literature spanning the last 10 years. We included studies on NAFLD in children and adolescents. The terms "NAFLD," "children," "adolescents," "prevalence," "treatment," "hepatic steatosis," etc. were used in the search. We also looked through the reference lists of papers found during the initial search to determine whether there were any other studies that might be relevant. The search was limited to publications in English, children and adolescents under 19 years old, clinical trials, case control studies, cross-sectional studies, and cohort studies. The authors independently vetted the titles and abstracts for inclusion in the review. Fig. 3 depicts the search technique as well as the selection criteria. The inclusion and exclusion criteria applied in the process of selecting studies for the meta-analysis are shown in Tab. 1.



NAFLD – non-alcoholic fatty liver disease; ***PNPLA3*** – patatin-like phospholipase domain-containing 3.

Fig. 1. Risk factors associated with NAFLD in children and adolescents

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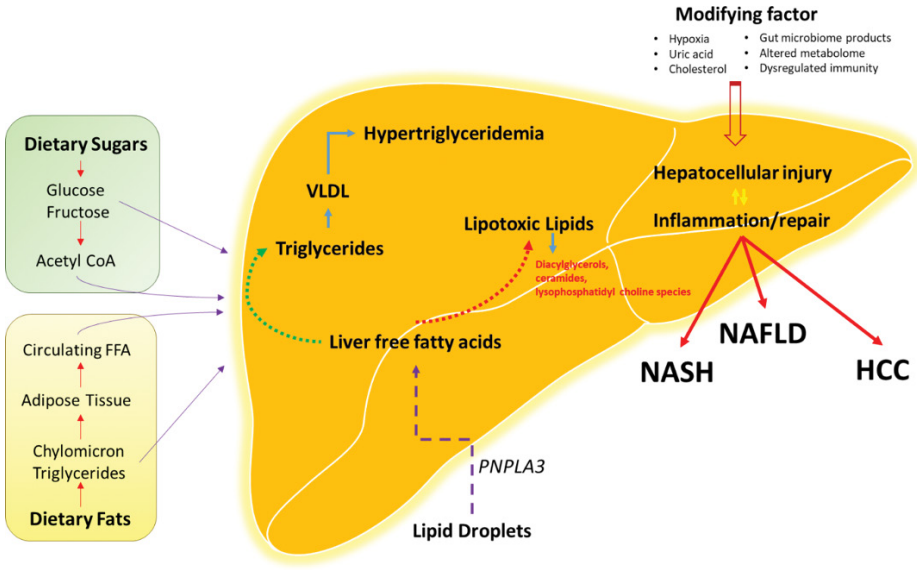

FFA – free fatty acids; **HCC** – hepatocellular carcinoma; **NAFLD** – non-alcoholic fatty liver disease; **NASH** – non-alcoholic steatohepatitis; ***PNPLA3*** – patatin-like phospholipase domain-containing 3; **VLDL** – very-low-density lipoprotein.

Fig. 2. Pathogenesis of NAFLD/NASH with excess dietary fats and sugars, adapted from Neuschwander-Tetri (2017)[10] and Mandala et al. (2020)[11]

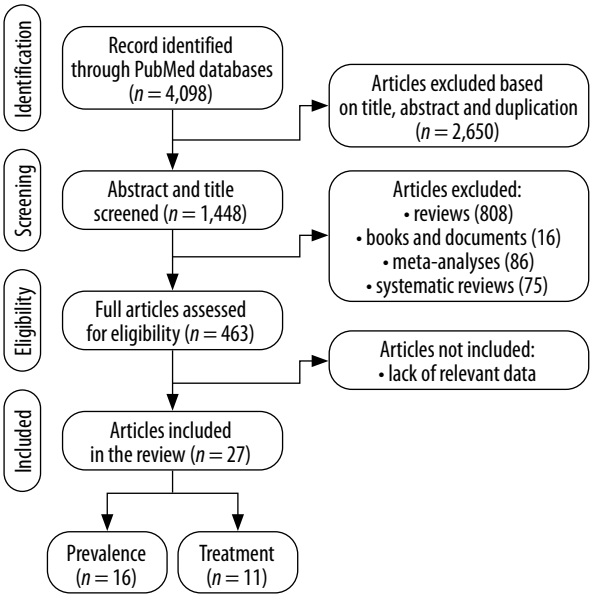

Fig. 3. Flowchart for the inclusion of study reports

Data analysis

The extracted data were analysed using Review Manager 5.4 with a 95% confidence interval. The random model was used to determine the heterogeneity among the studies, and forest plots were developed for the determination of the overall combined effects.

RESULTS

Following the initial search, a total of 4,098 articles were identified (Fig. 3). The titles and abstracts of the articles were screened, after which 2,650 articles were excluded from the study. The remaining 1,448 articles were carefully screened, and further screened for research purposes, thus excluding a further 985 articles, including reviews, books/papers, meta-analyses and systematic reviews. Four hundred and sixty-three (463) articles that were assessed for relevance and articles reporting original studies related to prevalence and treatment options remained and were included in the study. In total, 16 manuscripts related to prevalence and 11 related to treatment were selected from the articles spanning the last 10 years to perform this meta-analysis.

Inclusion	Exclusion
Original articles	Reviews
Case-control studies	Meta-analyses
Cross-sectional studies	Systematic reviews
Cohort studies	Books/documents
NAFLD in children and adolescents	NAFLD in adults (age >19 years)

NAFLD – non-alcoholic fatty liver disease.

Tab. 1. Criteria for the inclusion and exclusion of studies in the meta-analysis

All selected prevalence studies were published during the last 10 years and included a total of 27,241 children and adolescents with a pooled mean prevalence of 22.64%. The sample size ranged from 33 to 7,759, with a median of 728 per study. The combined effect of prevalence was determined by a random model with the odds ratio and a 95% confidence interval. There was a marked heterogeneity among the studies (I^2 = 43%). Overall, there was a significant difference ($p < 0.00001$) in NAFLD prevalence among children and adolescents (Fig. 4). From all selected studies, 11 studies showed a greater prevalence of NAFLD in adolescents compared to children (Fig. 4).

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Study of subgroup	Weight	Odds ratio M-H, random, 95% confidence interval	Odds ratio M-H, random, 95% confidence interval
Alkassabany et al., 2014[15]	7.4%	1.10 [0.21, 5.87]	
Ayonrinde et al., 2011[16]	6.0%	0.08 [0.01, 0.58]	
Yu et al., 2019[17]	8.5%	0.07 [0.02, 0.31]	
Ezaizi et al., 2019[18]	6.1%	0.04 [0.00, 0.26]	
Gupta et al., 2011[19]	8.3%	0.13 [0.03, 0.57]	
Jimenez-Rivera et al., 2017[20]	5.7%	0.01 [0.00, 0.07]	
Kang et al., 2018[21]	5.7%	0.17 [0.02, 1.38]	
Malespin et al., 2015[22]	5.7%	0.16 [0.02, 1.37]	
Mohamed et al., 2020[23]	6.0%	0.01 [0.00, 0.11]	
Park et al., 2020[24]	5.9%	0.09 [0.01, 0.70]	
Peña-Vélez et al., 2020[25]	6.1%	0.01 [0.00, 0.06]	
Sae-Wong et al., 2021[26]	5.8%	0.08 [0.01, 0.67]	
Conjeevaram Selvakumar et al., 2018[27]	5.8%	0.12 [0.02, 1.00]	
Song et al., 2017[28]	5.9%	0.11 [0.01, 0.87]	
Yang et al., 2020[29]	5.5%	0.25 [0.03, 2.24]	
Zhang et al., 2015[30]	5.6%	0.20 [0.02, 1.71]	
Total (95% CI)	**100.0%**	**0.08 [0.04, 0.16]**	
Total events			
Heterogeneity: Tau^2 = 0.73; Chi^2 = 26.16; *df* = 15 (p = 0.04); I^2 = 43% Test for overall effect: Z = 7.51 (p < 0.00001)			

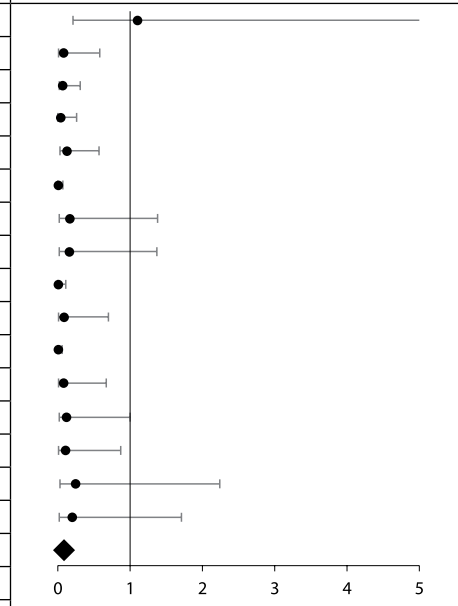

Fig. 4. Forest plot from the prevalence of NAFLD in children and adolescents

Author(s), year	Location	*N*	Diagnostic method
Alkassabany et al., 2014[15]	Egypt	800	ALT
Ayonrinde et al., 2011[16]	Australia	1,170	Ultrasound
Yu et al., 2019[17]	United States	408	MRI and ALT
Ezaizi et al., 2019[18]	United States	344	ALT
Gupta et al., 2011[19]	United States	655	ALT
Jimenez-Rivera et al., 2017[20]	Canada	97	Ultrasound and biochemical method
Kang et al., 2018[21]	Korea	1,416	ALT
Malespin et al., 2015[22]	United States	407	ALT
Mohamed et al., 2020[23]	Malaysia	33	Ultrasound
Park et al., 2020[24]	Korea	4,448	ALT
Peña-Vélez et al., 2020[25]	Mexico	112	Ultrasound
Sae-Wong et al., 2021[26]	Thailand	50	ALT
Conjeevaram Selvakumar et al., 2018[27]	United States	1,482	ALT
Song et al., 2017[28]	China	831	ALT
Yang et al., 2020[29]	China	7,759	Ultrasound
Zhang et al., 2015[30]	China	7,229	Ultrasound
ALT – alanine transaminase; **MRI** – magnetic resonance imaging.			

Tab. 2. Details of diagnostic methods used to estimate the prevalence of NAFLD in children and adolescents

The most widely used method for the estimation of prevalence among selected studies was the level of alanine transaminase (ALT) (10/16, 62.5% of studies). Ultrasound (5/16, 31.25 studies) was the second most prevalent method, followed by magnetic resonance imaging (MRI) (1/16, 6.25% studies), used for the diagnosis of NAFLD (Tab. 2). However, two studies reported the use of combined diagnostic tools (MRI and ALT; ultrasound and biochemical method) for determining the prevalence of NAFLD. Details of study location, number of participants (*N*), and diagnostic methods are presented in Tab. 2. Most of the selected studies were from Asian countries (China, Korea, Malaysia, and Thailand) with the involvement of 21,766 children and adolescents, and reporting an overall mean prevalence of 15.58% for NAFLD. Studies conducted in the US involved a total of 3,296 children/adolescents with the overall mean prevalence of 16.30% for NAFLD (Tab. 2).

Various strategies were adopted in different studies for the treatment of NAFLD in children and adolescents. We selected body mass index (BMI), ALT and aspartate transaminase (AST) levels from eligible studies to check the efficacy of interventions before and after trial. The combined effect of BMI by using a random model was 1.71 (0.25, 3.17), and the heterogeneity described with I^2 = 84%. Overall there was a non-significant difference in BMI values (p = 0.02) among the selected studies (Fig. 5). However, the combined effect of ALT by using a random model was 13.52 (7.28, 19.76), with heterogeneity I^2 = 93%. Eight studies in the forest plot showed a significant drop in ALT levels after treatment. There was a considerable difference in pooled ALT values (p < 0.00001) among the selected studies, which proved the beneficial effects of interventions on the NAFLD status in children and adolescents. The combined effect of AST by using a random model was 6.24 (0.62, 11.86), with heterogeneity I^2 = 91%. Among the selected studies, three reported a significant drop in the AST level, though overall there was a non-significant difference in AST values (p = 0.03) across the selected studies (Fig. 5).

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Study or subgroup	Before treatment			After treatment			Weight	Mean difference
	Mean	*SD*	Total	Mean	*SD*	Total		IV, random, 95% confidence interval
1.1.1 BMI								
Antunes Bde et al., 2013[31]	29.5	5.1	34	28.9	3.4	34	5.5%	0.60 [−1.46, 2.66]
Boyraz et al., 2015[32]	29.7	4.8	52	23.7	3.5	52	5.7%	6.00 [4.39, 7.61]
Chan et al., 2018[33]	32.59	3.28	26	31.8	2.01	26	5.7%	0.79 [−0.69, 2.27]
Farris et al., 2011[34]	30.31	4.56	25	27.8	4.54	25	5.3%	2.51 [−0.01, 5.03]
Goss et al., 2020[35]	38.4	7.3	16	37.6	5.5	16	4.2%	0.80 [−3.68, 5.28]
Grønbæk et al., 2012[36]	2.93	0.52	117	2.49	0.75	71	6.0%	0.44 [0.24, 0.64]
Pacifico et al., 2015[37]	27.2	5.4	29	27.3	4.1	29	5.3%	−0.10 [−2.57, 2.37]
Santomauro et al., 2012[38]	28.25	4.23	24	27.9	5.17	24	5.2%	0.35 [−2.32, 3.02]
Sundaram et al., 2018[39]	33.7	6.3	23	29.5	3.9	9	4.7%	4.20 [0.58, 7.82]
Subtotal (95% CI)			**346**			**286**	**47.5%**	**1.71 [0.25, 3.17]**
Heterogeneity: $Tau^2 = 3.54$; $Chi^2 = 51.57$; $df = 8$ ($p < 0.00001$); $I^2 = 84\%$ Test for overall effect: $Z = 2.30$ ($p = 0.02$)								
1.1.2 ALT								
Boyraz et al., 2015[32]	58.2	17.7	52	32.4	4.6	52	3.9%	25.80 [20.83, 30.77]
Chan et al., 2018[33]	38.9	25.6	26	5.41	22.63	26	1.3%	33.49 [20.36, 46.62]
Famouri et al., 2017[40]	32.8	19.6	32	24.3	7.7	32	2.8%	8.50 [1.20, 15.80]
Farris et al., 2011[34]	41.7	9.8	25	35.0	8.5	25	3.9%	6.70 [1.61, 11.79]
Goss et al., 2020[35]	57.7	36.6	16	52.9	40.5	16	0.4%	4.80 [−21.95, 31.55]
Grønbæk et al., 2012[36]	213.0	74.0	117	184.0	74.0	71	0.5%	29.00 [7.18, 50.82]
Koot et al., 2011[41]	28.2	12.6	144	22.6	6.6	144	5.4%	5.60 [3.28, 7.92]
Pacifico et al., 2015[37]	42.0	22.0	29	27.0	14.0	29	2.1%	15.00 [5.51, 24.49]
Santomauro et al., 2012[38]	13.63	2.67	24	12.29	2.05	24	5.8%	1.34 [−0.01, 2.69]
Sundaram et al., 2018[39]	169.0	179.0	23	90.0	28.0	9	0.0%	79.00 [3.59, 154.41]
Subtotal (95% CI)			**488**			**428**	**26.1%**	**13.52 [7.28, 19.76]**
Heterogeneity: $Tau^2 = 67.08$; $Chi^2 = 126.31$; $df = 9$ ($p < 0.00001$); $I^2 = 93\%$ Test for overall effect: $Z = 4.25$ ($p < 0.0001$)								
1.1.3 AST								
Boyraz et al., 2015[32]	43.3	13.3	52	29.8	5.6	52	4.5%	13.50 [9.58, 17.42]
Chan et al., 2018[33]	22.5	7.8	26	7.4	11.27	26	3.8%	15.10 [9.83, 20.37]
Famouri et al., 2017[40]	32.2	15.7	32	32.8	19.6	32	2.3%	−0.60 [−9.30, 8.10]
Farris et al., 2011[34]	30.6	8.2	25	35.0	8.5	25	4.1%	−4.40 [−9.03, 0.23]
Goss et al., 2020[35]	35.5	18.4	16	28.1	17.8	16	1.4%	7.40 [−5.14, 19.94]
Koot et al., 2011[41]	31.2	21.2	144	22.8	12.7	144	4.5%	8.40 [4.36, 12.44]
Santomauro et al., 2012[38]	12.17	2.51	24	11.25	2.51	24	5.7%	0.92 [−0.50, 2.34]
Sundaram et al., 2018[39]	100.0	114.0	23	59.0	16.0	9	0.1%	41.00 [−6.75, 88.75]
Subtotal (95% CI)			**342**			**328**	**26.4%**	**6.24 [0.62, 11.86]**
Heterogeneity: $Tau^2 = 48.78$; $Chi^2 = 76.26$; $df = 7$ ($p < 0.00001$); $I^2 = 91\%$ Test for overall effect: $Z = 2.18$ ($p = 0.03$)								
Total (95% CI)			**1,176**			**1,042**	**100.0%**	**5.23 [3.55, 6.92]**
Heterogeneity: $Tau^2 = 12.38$; $Chi^2 = 315.27$; $df = 26$ ($p < 0.00001$); $I^2 = 92\%$ Test for overall effect: $Z = 6.08$ ($p < 0.00001$) Test for subgroup differences: $Chi^2 = 14.82$; $df = 2$ ($p = 0.0006$); $I^2 = 86.5\%$								

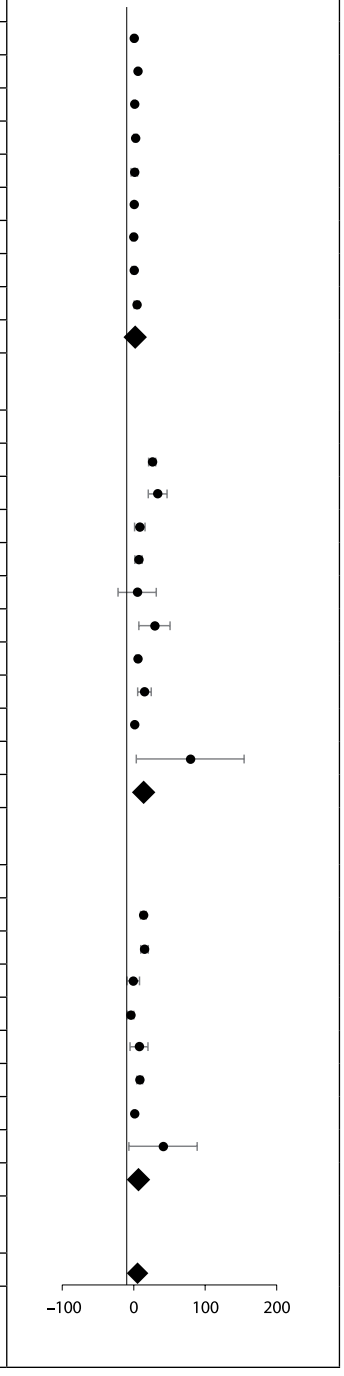

Fig. 5. Effects before and after treatment/intervention on BMI, ALT and AST levels

The overall combined effect of all subgroups (BMI, ALT and AST) indicated a significant difference among the studies (Fig. 5).

Details of treatments/interventions used in each study for NAFLD in children and adolescents are listed in Tab. 3. Out of the selected studies, six were controlled trials, four were clinical trials, and one was a non-randomised controlled trial. Most of the studies involved lifestyle intervention including exercise and diet change. One study reported the use of polyunsaturated fatty acids (PUFA) along with lifestyle modification as a safe and efficacious treatment in obese children with NAFLD. Improvements in ultrasonographic findings and transaminase levels have also been reported. Chan et al.[33] found that a dietitian-led lifestyle modification intervention reduced the intra-hepatic triglyceride content and body fat in obese Chinese adolescents

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Author(s), year	Location	*N*	Type of intervention/treatment	Frequency and duration of intervention
Antunes Bde et al., 2013[31]	Brazil	34	Concurrent physical training (combination of weight training with aerobic training)	Three times per week. One hour, for a total of 20 weeks
Boyraz et al., 2015[32]	Turkey	180	Polyunsaturated fatty acids (PUFA) and lifestyle intervention	1,000 mg dose of PUFA once daily for 12 months
Chan et al., 2018[33]	China	52	Dietitian-led lifestyle modification programme (D-LMP)	Weekly for 16 weeks and bimonthly visits for dietary advice for 52 weeks
Famouri et al., 2017[40]	Iran	64	Probiotic capsules for 12 weeks	One probiotic capsule administered daily for 12 weeks
Farris et al., 2011[34]	United States	25	Aerobic and resistance exercise appropriate to age and developmental levels	Three days each week for a total of 12 weeks
Goss et al., 2020[35]	United States	32	Carbohydrate-restricted diet (CRD) vs. fat-restricted diet (FRD)	Eight weeks
Grønbæk et al., 2012[36]	Denmark	117	Weight loss camp	Three healthy meals per day at fixed time points, with breakfast, lunch, and an evening meal, for a total of 10 weeks
Koot et al., 2011[41]	Netherlands	144	Lifestyle intervention programme	Scheduled exercise (three times per week for one hour), for a total of six months
Pacifico et al., 2015[37]	Italy	51	Treatment with docosahexaenoic acid	Six months
Santomauro et al., 2012[38]	Venezuela	36	12-month lifestyle intervention	12 months
Sundaram et al., 2018[39]	United States	32	Treatment with continuous positive airway pressure (CPAP)	89 ± 62 days

Tab. 3. Details of NAFLD treatments/interventions used in each study in children and adolescents

with NAFLD. One of the selected studies reported the use of probiotic capsules as an effective modality in improving the paediatric NAFLD status. The intervention with carbohydrate-restricted diet and fat-restricted diet in adolescents with NAFLD was found to result in decreased hepatic lipid levels as well as improvements in body composition and insulin resistance. Another study reported the use of docosahexaenoic acid that decreased liver and visceral fat, and ameliorated metabolic abnormalities in children with NAFLD.

DISCUSSION

NAFLD is the most prevalent liver disease in the world, and it has become a major public health concern. Despite the widespread knowledge of the pathogenic pathways that contribute to overweight and obesity, both of which are important risk factors for NAFLD, the incidence of this insidious illness is rising in children and adolescents aged 1–19 years. Obesity and overweight have become the most common causes of liver diseases in children[42,43]. The majority of people with NAFLD present with no symptoms. However, if a child's or adolescent's waist circumference is in the 95th percentile for their age and gender, NAFLD should be investigated[44]. It must be searched for actively in high-risk children, such as those who are overweight or obese, or those who have dyslipidaemias, insulin resistance, or type 2 diabetes mellitus. As no ideal screening test exists at this time, the first examination should be alanine aminotransferase (ALT) determination, which should begin at the age of nine years[45]. In this meta-analysis, we have reviewed different studies reporting on the prevalence and treatment strategies for NAFLD in children and adolescents. Among the selected studies related to the prevalence data, there was a marked heterogeneity (I^2 = 43%), as shown in Fig. 4. However, the results of our study also show a significant difference ($p < 0.00001$) in NAFLD prevalence among children and adolescents. These findings are in line with previously reported studies[42,46]. In the present study, we also found that the pooled mean prevalence was 22.64%, which is similar to the NAFLD prevalence reported in the general population, with the range of 9–37%[46,47]. However, more studies reported a greater prevalence of the condition in adolescents as compared to children. The reported higher prevalence in adolescents might be due to more limited involvement of children in those studies or the sedentary lifestyle of adolescents making them overweight and obese. NAFLD may be assessed and diagnosed using several ultrasound or MRI techniques[45]. Aminotransferases have been shown to be inaccurate markers of steatosis when used to screen for NAFLD; as ALT elevation beyond twice the upper limit of normal has a sensitivity of 57% and a specificity of 71% in this context[48]. Liver biopsy should also be performed in children with an unclear diagnosis or indications of severe fibrosis, splenomegaly, and an elevated ratio of AST/ALT > 1[45]. In this meta-analysis, the most commonly utilised technique for estimating NAFLD prevalence across the selected studies was detection of the ALT level (10/16, 62.5% studies). However, ultrasonography (5/16, 31.25% studies) was the second most widely used technique for diagnosing NAFLD, followed by MRI (1/16, 6.25% studies). Biochemical and imaging techniques are commonly employed to diagnose NAFLD, as liver biopsies are invasive. In our search, only a few studies used MRI, which is also reported as a modality for the diagnosis and prevalence of NAFLD by Awai et al.[49]. The findings of biopsy/histology, which is considered to be the gold standard for detecting and quantifying hepatic steatosis in the context of NAFLD, were not mentioned in any of the selected studies to report the prevalence. Because of the paucity of histology data, researchers are unable to investigate the impact of lifestyle modifications on hepatic fibrosis, which is a key predictor of long-term outcomes[50]. The precise and accurate diagnosis

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of NAFLD at earlier stages is necessary to treat/control the disease in children, adolescents, and even in adults.

As NAFLD is linked to obesity, the first step in therapy/treatment is to encourage lifestyle modifications, such as increased physical activity and improved diet among children and adolescents. In fact, physical activity appears to decrease steatosis even without weight reduction. Isolated exercise without calorie restriction has yet to be proved to be helpful[38,41,51]. The main objective of NAFLD therapy is to eliminate steatosis and/or liver fibrosis. A decrease in ALT is commonly viewed as a marker of progress in NAFLD treatment[4]. To achieve a long-term success in the therapy of NAFLD, a combination of cognitive-behavioural methods, family and community-based treatments, and telemedicine should be used[52]. In this meta-analysis, changes in BMI and aminotransferase (ALT and AST) levels were adopted as outcome measures after the treatment/intervention because these are the indicators most commonly used in paediatric interventional studies in the field of NAFLD and frequently applied for evaluation in the clinical setting. The combined effect of BMI by using a random model was 1.71 (0.25, 3.17) and heterogeneity described with the I^2 value was 84%. However, an overall non-significant difference was observed in BMI values ($p = 0.02$) among the selected studies (Fig. 5). The combined effect of ALT by using a random model was 13.52 (7.28, 19.76) and heterogeneity determined with the I^2 value was 93%. Subsequently, eight studies in the forest plot showed a significant drop in ALT levels after treatment, and there was a significant difference in pooled ALT values ($p < 0.00001$) among the selected studies, which proved the beneficial effects of interventions on the NAFLD status in children and adolescents. The results also indicated a significant decrease in hepatic steatosis accompanied by ALT changes, though no change in BMI values was observed across the selected studies. The latter finding may be due to the limitations of BMI as a proxy measure of obesity. Similarly, Antunes Bde et al.[31] looked at the influence of physical exercise on NAFLD and found that there was a non-significant difference in BMI values. The combined effect of AST was also assessed in this study by using a random model with the heterogeneity of 91%. Among the selected studies related to AST, three studies reported a significant drop in the AST level, though the overall difference in AST values ($p = 0.03$) among the selected studies was non-significant (Fig. 5). That might be due to the genetic and demographic differences among the population included in different studies.

In this meta-analysis, most of the studies involved lifestyle interventions including exercise and diet change[31,38,41], which generally appears to indicate weight loss as a key component in lowering the risk of NAFLD. Even when various values for weight loss are shown, there is a positive interference in this disease. One study included in this meta-analysis reported the use of PUFA along with lifestyle modification as a safe and efficacious treatment modality in obese children with NAFLD. An improvement in ultrasonographic findings and transaminase levels has also been reported[32]. Chan et al.[33] reported that a dietitian-led lifestyle modification intervention reduced the level of intra-hepatic triglyceride content and body fat in obese Chinese adolescents with NAFLD. One of the selected studies also reported the use of probiotic capsules as a modality that can effectively reduce the prevalence of paediatric NAFLD[40]. In another study, an intervention with carbohydrate-restricted diet and fat-restricted diet in adolescents with NAFLD resulted in decreased hepatic lipid levels as well as improvements in body composition and insulin resistance[35]. Subsequently, the use of docosahexaenoic acid decreased liver and visceral fat, and ameliorated metabolic abnormalities in children with NAFLD[37]. Adult studies also suggested that changing one's lifestyle might help with NAFLD treatment[4,45]. According to this in-depth review and meta-analysis, a balanced diet paired with physical activity improves BMI, aminotransferases, and hepatic steatosis in children and adolescents with NAFLD, regardless of puberty status[38,53].

Prevention is the most important element in decreasing the prevalence of NAFLD in children, and therefore also in adults. In addition to paediatricians and nutritionists who are already working with obese children, programs must engage families and the community[52] to implement effective strategies for controlling NAFLD among children and adolescents. Genetic screening programs for NAFLD must be started as soon as possible after birth, ideally during the perinatal period[9] to identify potential genetic problems. In addition, children/adolescents should be tested for ALT or examined by imaging tools to determine the disease status once a year[54]. In addition, specific follow-up studies must be designed to determine the success rate of interventions for developing future guidelines. To ensure long-term success, routine prevalence studies should be conducted with more detailed examination of individual-level factors and their interrelationships, and new non-invasive, accurate and specific diagnostic tools for the detection of NAFLD in children/adolescents must be developed. Furthermore, multidisciplinary teams of experts should work together to develop treatment strategies, and more randomised controlled studies are needed to explore the impact of lifestyle interventions and other treatments on the histology of patients with NAFLD.

CONCLUSION

In conclusion, NAFLD is quite common among children and adolescents. Prevention is the most important element in decreasing the prevalence of NAFLD in children. Lifestyle modification and other therapeutic techniques are known to have a substantial effect on reducing the occurrence of the disease. Children and adolescents must be engaged in physical activities and have a well-balanced diet to prevent obesity and NAFLD. Furthermore, children should be tested for ALT or examined by imaging tools to assess the degree of steatosis or fibrosis once a year. More randomised

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controlled studies are needed to explore the impact of lifestyle interventions and other treatments on different pathogenetic factors in patients with NAFLD.

Conflict of interest

All authors declare no conflict of interest.

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