Original Article

Relationship between obesity related indicators and non-alcoholic fatty liver disease in children: a systematic review and meta-analysis

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Background: The incidence of childhood obesity is increasing. There is some controversy about the association between overweight and nonalcoholic fatty liver disease (NAFLD) in children. This article intends to compare the differences in these obesity related parameters between NAFLD children and healthy control children through meta-analysis to provide evidence-based medical evidence for clinical use.

Methods: The literature were extracted from English and Chinese databases. Statistical analysis was performed using Stata/SE 16.0, IBM SPSS Statistics 26, and Review Manager 5.4 software.

Results: A total of 15 original case control studies were included, including 12 high-quality literature, 3 medium quality literature. The total sample size included in the analysis was 1,595 children, including 824 in the experimental group and 771 in the control group. The results of meta-analysis showed that the body mass index (BMI) of the NAFLD group was significantly higher than that of the control group [mean difference (MD) =1.05, 95% confidence interval (CI): 0.36–1.73]. Waist circumference of the NAFLD group was significantly larger than that of the control group (MD =1.66, 95% CI: 0.60–2.73). Triglyceride level in the NAFLD group was significantly higher than that in the control group (MD =1.08, 95% CI: 0.05–2.12). Low-density lipoprotein (LDL) level in the NAFLD group was significantly higher than that in the control group (MD =0.49, 95% CI: 0.12–0.85). In addition, fasting blood glucose of the NAFLD group was significantly higher than that of the control group (MD =0.31, 95% CI: 0.09–0.54) and insulin resistance index of the NAFLD group was significantly higher than that of the control group (MD =2.95, 95% CI: 1.41–4.49). Exercise had a significant effect on improving the degree of NAFLD in children [odds ratio (OR) =2.51, 95% CI: 1.83–3.43].

Conclusions: Various physical indicators were related to obesity, including BMI, waist circumference, triglyceride content, LDL, fasting blood glucose, and insulin resistance index, and all were significantly correlated with NAFLD in children, provided a reference for future clinical diagnosis and treatment work. In addition, exercise could significantly improve the degree of steatosis in children with NAFLD.

Keywords: Nonalcoholic fatty liver disease (NAFLD); children; obesity; exercise

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Introduction

Over the past two decades, childhood obesity has skyrocketed to alarming levels (1). This increase is attributed to socioeconomic progress and better nutritional status for children. Obesity is linked to metabolic syndrome, a condition that includes health problems such as central obesity, high blood pressure, insulin resistance, and abnormal cholesterol levels. These issues can result in cardiovascular disease and type 2 diabetes, posing serious threats to the well-being of adolescents and children (2,3).

Nonalcoholic fatty liver disease (NAFLD) is a clinical condition characterized by the degeneration of over 5% of liver cells, which is not caused by alcohol consumption or other specific factors. This leads to chronic fat accumulation in the liver (4). The worldwide prevalence of NAFLD now exceeds 25%, and due to the rising rates of obesity and changes in lifestyle, it is expected to become the most common liver disease within the next decade (5). The global incidence of NAFLD among children and adolescents currently ranges from 3% to 10% (6). For this population, NAFLD can significantly heighten the risk of severe cardiovascular events in adulthood, such as diabetes, chronic kidney disease, and stroke (7). Consequently, early prevention and intervention for NAFLD in children and adolescents are crucial for enhancing their health and reducing the medical burden later in life.

Factors such as prolonged sitting, physical activity, high sugar diet, intestinal health flora imbalance, and prenatal environment are also associated with the onset of nonalcoholic fatty liver disease in children. A large number of studies have reported the relationship between overweight and NAFLD in children (7-11), however, there is significant heterogeneity among these studies, with different inclusion criteria, observation indicators, and outcomes. Therefore, there are still some controversies regarding the specific relationship between overweight and NAFLD in children. In addition, a standard, evidence-based screening method for NAFLD in obese children is still lacking (9). In addition, nondrug treatment of NAFLD in children is particularly important. However, the most important of the non-pharmacological treatments, exercise, has been studied for its effectiveness in improving NAFLD in children, with mixed results and a lack of systematic analysis. This meta-analysis summarized, analyzed, and compared overweight-related body parameters [height, weight, body mass index (BMI), and waist circumference], related lipid metabolism parameters [total cholesterol, triglyceride, high-density lipoprotein (HDL), and low-density lipoprotein (LDL)], and glucose metabolism parameters (fasting blood glucose and insulin resistance index) of children with NAFLD and healthy children, and the differences in these overweight-related parameters between children with NAFLD and healthy control children were compared. The relationship between overweight and the onset of NAFLD in children was thus established, thus contributing to the early detection, diagnosis and treatment of NAFLD. We also evaluated the effect of exercise on the degree of NAFLD (0–3) in children, providing new insights for nondrug treatment of NAFLD in children. We present the following article in accordance with the MOOSE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-123/rc).

Highlight box

Key findings

- All body indicators related to obesity had a certain predictive effect on NAFLD in children, and exercise could significantly improve the degree of fatty degeneration in children with NAFLD.

What is known and what is new?

- A standard, evidence-based NAFLD screening method for obese children is currently lacking.
- This meta-analysis summarized and compared obesity body parameters, lipid metabolism parameters, and glucose metabolism parameters in children with NAFLD and healthy children.

What is the implication, and what should change now?

- In this study, the relationship between obesity and NAFLD in children was determined, providing a reference range of obesity-related parameters for the early screening of NAFLD in children, thereby contributing to the early detection, diagnosis, and treatment of NAFLD.

Methods

Literature search strategy

This meta-analysis was conducted in strict accordance with PICOS principles. We extracted English and Chinese literature published form the establishment of the databases to December 2022 from PubMed, Embase, Scopus, China National Knowledge Infrastructure (CNKI), Chongqing VIP Information (VIP), Wanfang databases by adopting a combination of subject terms and unrestricted search. The Chinese and English search terms included “obesity” (OR “overweight” OR “fat”), “diabetes mellitus” (OR “diabetes”

OR "glycuresis" OR "insulin resistance"), "exercise" (OR "sports"), "pediatrics" (OR "children" OR "child"), and "Nonalcoholic fatty liver disease" (OR "NAFLD"). This study also checked citation indexes and reference lists of retrieved articles for additional studies not identified in the original database search.

Inclusion and exclusion criteria

Inclusion criteria

(I) Population: children under the age of 18.
(II) Intervention or Observation indicators: participants' weight, height, BMI, waist circumference, total cholesterol, triglyceride content, LDL, HDL, fasting blood glucose, insulin resistance index (homeostasis model assessment of insulin resistance (HOMA-IR)].
(III) Comparison: the NAFLD group was defined as children who were clinically diagnosed according to international standards through methods such as liver ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and biopsy, and who had no comorbidities; the control group was defined as healthy children without any underlying disease.
(IV) Outcomes: diagnosis of nonalcoholic fatty liver disease, and degree of fatty liver (0–3), with no missing data.
(V) Study design: case control study, the full text of which was available.

Exclusion criteria

(I) Duplicate articles or no full text.
(II) Studies with missing data or errors that could not be completed or corrected.
(III) Lack of outcome indicators needed for this study.
(IV) Children with any other diseases.
(V) Letters, case reports, comments, and practical guidelines, etc.
(VI) Studies that did not diagnose NAFLD according to international standards or did not exclude other causes of chronic liver disease (alcohol consumption, chronic viral hepatitis, metabolic liver disease, hereditary hemochromatosis, secondary hepatic steatosis drugs, or liver toxic drugs, etc.).
(VII) All animal experiments.

Outcome indicators

The outcome indicators included: weight, height, BMI, waist circumference, total cholesterol, triglyceride content, LDL, HDL, fasting blood glucose (mg/dL), insulin resistance index (HOMA-IR), and fatty liver classification (0–3) of children in the NAFLD group and the healthy control group.

Data extraction

We collected the following data: article title, first author, year of publication, country of study, type of study design, sample size of experimental and control groups, mean age of experimental and control samples and their standard deviation (if available), and relevant outcomes index.

Quality evaluation

The quality of the studies was assessed by 2 independent researchers and based on the Newcastle-Ottawa Scale (NOS) (12). When opinions differed, discussions were held with a third party to reach agreement. NOS includes 8 items, specifically including study population selection, comparability, exposure evaluation, or outcome evaluation. The total score is 9 points, with 1–3, 4–6, and 7–9 points being low, medium, and high-quality, respectively, with a high, medium, and low risk of bias.

Statistical analysis

Statistical analysis was conducted using Stata/SE 16.0, IBM SPSS Statistics 26, and Review Manager 5.4 software. Weight, height, BMI, waist circumference, total cholesterol value, triglyceride content, LDL content, HDL content, fasting blood glucose, insulin resistance index (HOMA-IR), and fatty liver grade (0–3) were analyzed. Except for fatty liver grade, outcome indicators were continuous variables and represented by the mean and its 95% confidence interval (CI). The Q test was used to assess heterogeneity between studies. I^2<50% and P>0.1 indicated that the heterogeneity between the studies was small, and the fixed-effect model was used. Conversely, the random-effects model was used to calculate the size of the combined effect size. As fatty liver disease was a categorical ordinal variable, and therefore differs from a dichotomous variable such as cure/exacerbation of disease, we were not able to calculate the combined effects directly using Stata/SE 16.0 software to calculate the relative risk. Logistic regression was first used to calculate the effect size of each included study and its standard error, followed by the generic inverse variance

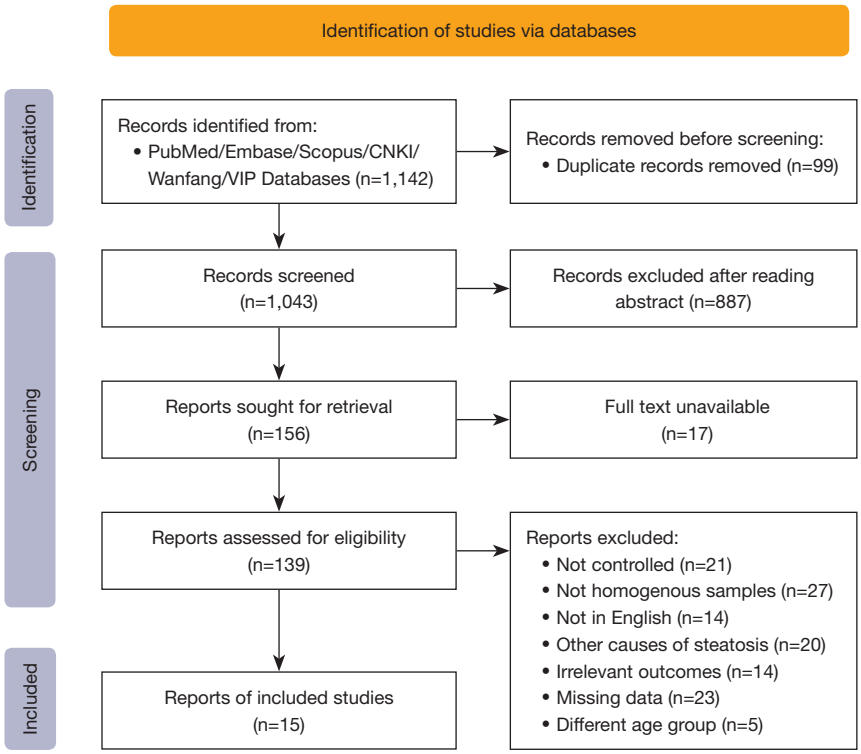

Figure 1 Flow chart of literature screening.

method in Review Manager 5.4 to combine the effect size for meta-analysis. The statistical results of meta-analysis are depicted by forest plots. Funnel plots were drawn to evaluate publication bias, and the Begg's test was used to further evaluate publication bias. P<0.05 was considered statistically significant.

Results

Literature search screening results

A total of 1,142 studies were extracted from the databases through the above retrieval methods. By browsing titles, keywords, and abstracts, 156 of these studies were identified as potentially relevant to the research topic. Of these 156 studies, we obtained the full text of 139 studies. Based on the inclusion and exclusion criteria, we excluded a further 124 studies. Ultimately, a total of 15 studies (13-27) were included in this meta-analysis. The document screening process is shown in *Figure 1*.

Basic characteristics of included studies

All 14 included studies were original. The total sample comprised 1,595 children, including 824 in the experimental group and 771 in the control group. The basic characteristics of the included studies are listed in *Table 1*.

Quality assessment of included literature

The quality of the studies was evaluated based on NOS, with scores ranging from 0–9 points. Studies with 1–3, 4–6, and 7–9 are low, medium, and high quality research, respectively, with high, medium, and low bias risks. The meta-analysis included 12 high-quality documents, 3 medium quality documents, and 0 low quality documents. The quality evaluation results of the included literature are shown in *Table 2*.

Meta analysis results and sensitivity analysis

Effect of body weight on the incidence of NAFLD in children

The results of the heterogeneity test of the included studies were: I^2=58.80%, P=0.06, and thus the random-effects model was used for meta-analysis. The results showed that there was no statistically significant difference in body

Table 1 Basic characteristics of the included studies

Study (year)	Country	Type of study	Experimental group		Control group	
			Sample size	Age, years	Sample size	Age, years
Kurku, 2019	Turkey	Case-control	101	13.2±1.6	18	13.1±2.3
Malecki, 2020	Poland	Case-control	16	11.0±2.2	14	10.6±4.5
Kwon, 2020	Korea	Case-control	53	10.8±1.3	73	10.8±1.4
Thompson, 2017	USA	Case-control	20	13.2±3.1	10	13.8±2.1
Battal, 2018	Turkey	Case-control	32	13.3±2.8	24	12.8±3.3
Elkabany, 2020	Egypt	Case-control	31	9.98±3.39	49	8.3±2.73
Gupta, 2020	India	Case-control	62	10.52±2.2	38	9.32±2.4
Hattar, 2011	USA	Case-control	20	12.2±2	17	12.4±2.1
Hu W, 2017	China	Case-control	29	10.23±1.35	16	9.72±1.61
Liu F, 2022	China	Case-control	48	11.24±0.59	54	10.16±0.48
Antunes, 2013	Brazil	Clinical trial	34	13.6±1.1	34	13.6±1.0
Grønbæk H, 2012	Denmark	Clinical trial	117	12.3±1.3	117	12.1±1.3
Grønbæk H, 2012	Denmark	Clinical trial	71	13.4±1.3	117	12.1±1.3
Koot BG, 2011	The Netherlands	Clinical trial	144	14.1±2.3	144	14.1±2.3
Verduci, 2013	Italy	Clinical trial	46	6–14	46	6–14
Nier, 2018	Austria	Clinical trial	16	7.8±0.3	36	7.3±0.2

Data are shown as number, range, or mean ± standard deviation.

weight between children with NAFLD and healthy children [mean difference (MD) =0.31 kg, 95% CI: −0.07 to 0.69 kg; *Figure 2*]. Sensitivity analysis showed that deleting studies 1 by 1 would not significantly change the size of the overall effect, and the results were relatively stable.

Effect of height on the incidence of NAFLD in children

The results of the heterogeneity test of the included studies were: I^2=21.67%, P=0.28, and thus the fixed-effect model was used for meta-analysis. The results showed that there was no statistically significant difference in height between children with NAFLD and healthy children (MD =0.13 cm, 95% CI: −0.09 to 0.36 cm; *Figure 3*). Sensitivity analysis showed that deleting studies 1 by 1 would not significantly change the size of the overall effect, and the results were relatively stable.

The influence of body mass index on the incidence of NAFLD in children

The results of the heterogeneity test of the included studies were: I^2=91.18%, P<0.001, and thus the random-effects model was used for meta-analysis. The results showed that the BMI value of the NAFLD group was significantly higher than that of the control group (MD =1.05 kg/m^2, 95% CI: 0.36 to 1.73 kg/m^2) compared with healthy children (*Figure 4*). Sensitivity analysis showed that deleting studies 1 by 1 would not significantly change the size of the overall effect, and the results were relatively stable.

Effect of waist circumference on the incidence of NAFLD in children

The results of the heterogeneity test of the included studies were: I^2=95.18%, P<0.001, and thus the random-effects model was used for meta-analysis. The results showed that waist circumference of the NAFLD group was significantly larger than that of the control group (MD =1.66 cm, 95% CI: 0.60 to 2.73 cm) compared with healthy children (*Figure 5*). Sensitivity analysis showed that deleting studies 1 by 1 would not significantly change the size of the overall effect, and the results were relatively stable.

Effect of total cholesterol on the incidence of NAFLD in children

The results of the heterogeneity test of the included studies

Table 2 Quality evaluation of included studies

Included studies	Quality Review score (NOS)	Selection of research subjects				Comparability between groups	Outcome measurement		
		Experimental group representativeness	Control group representativeness	Definition of experimental group	Definition of control group		Outcome measures	Follow-up time	Completeness of follow-up
Kurku, 2019	9	Good	Good	Clear	Clear	Good	Low risk	Long	Good
Malecki, 2020	8	Uncertain	Good	Clear	Clear	Good	Low risk	Long	Good
Kwon, 2020	9	Good	Good	Clear	Clear	Good	Low risk	Long	Good
Thompson, 2017	6	Uncertain	Uncertain	Clear	Clear	Uncertain	Low risk	Long	Good
Battal, 2018	6	Good	Good	Clear	Uncertain	Uncertain	Uncertain	Long	Uncertain
Elkabany, 2020	8	Uncertain	Good	Clear	Clear	Good	Low risk	Long	Good
Gupta, 2020	7	Good	Good	Clear	Clear	Good	Uncertain	Long	Uncertain
Hattar, 2011	9	Good	Good	Clear	Clear	Good	Low risk	Long	Good
Hu W, 2017	8	Good	Uncertain	Clear	Clear	Good	Low risk	Long	Good
Liu F, 2022	8	Good	Good	Clear	Clear	Good	Uncertain	Long	Good
Antunes, 2013	4	Uncertain	Uncertain	Uncertain	Clear	Uncertain	Low risk	Uncertain	Good
Grønbæk H, 2012 (10 weeks)	7	Good	Good	Clear	Uncertain	Uncertain	Uncertain	Long	Good
Grønbæk H, 2012 (12 months)	8	Good	Good	Clear	Clear	Good	Low risk	Long	Uncertain
Koot BG, 2011	9	Good	Good	Clear	Clear	Good	Low risk	Long	Good
Verduci, 2013	8	Good	Good	Clear	Clear	Uncertain	Low risk	Long	Good
Nier, 2018	8	Good	Good	Clear	Clear	Uncertain	Low risk	Long	Good

NOS, Newcastle-Ottawa Scale

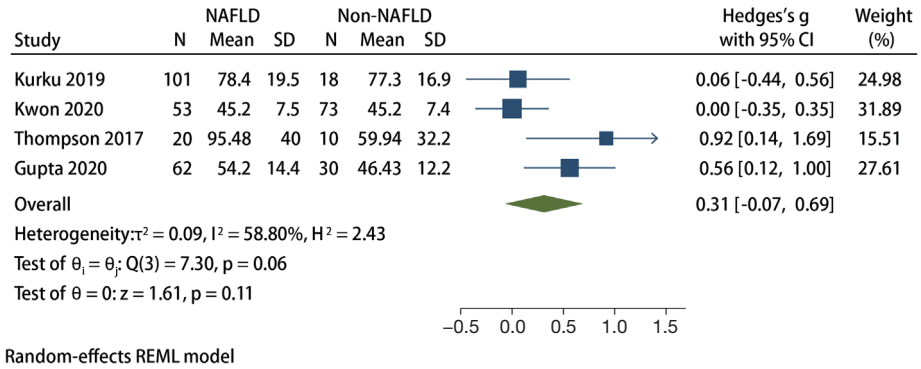

Figure 2 Forest plot of the impact of body weight on the incidence of NAFLD in children. NAFLD, nonalcoholic fatty liver disease; CI, confidence interval.

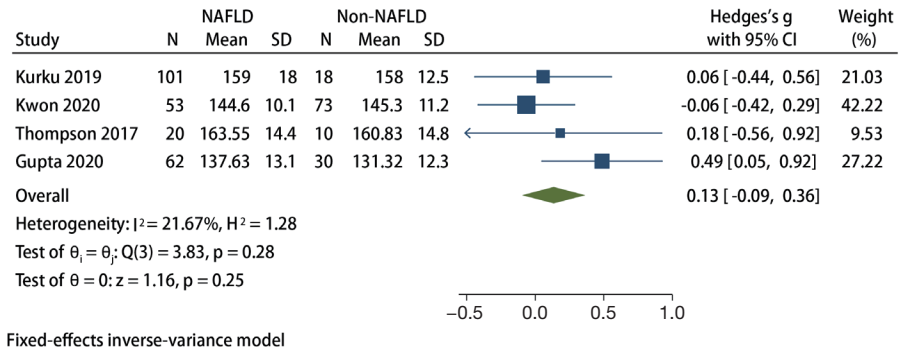

Figure 3 Forest plot of the effect of height on the incidence of NAFLD in children. NAFLD, nonalcoholic fatty liver disease; CI, confidence interval.

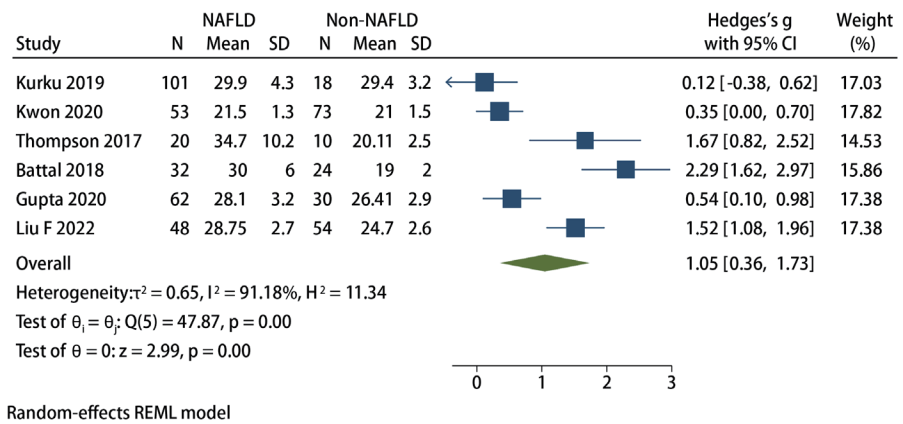

Figure 4 Forest plot of the impact of BMI on the incidence of NAFLD in children. BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; CI, confidence interval.

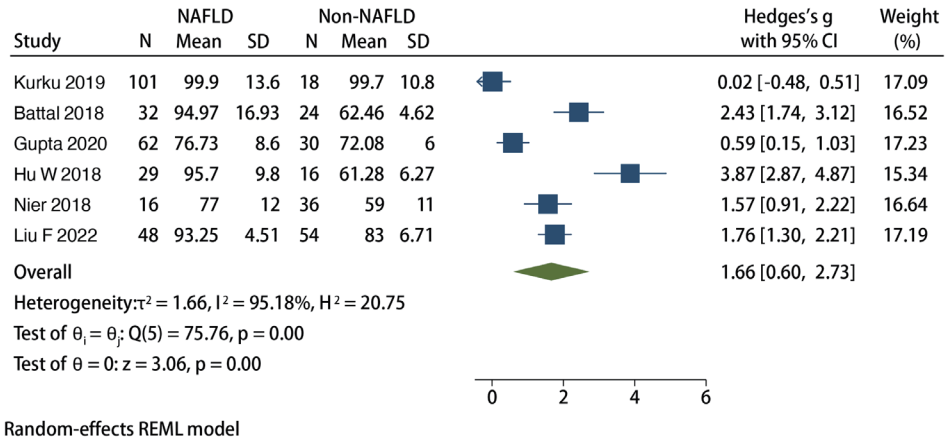

Figure 5 Forest plot of the impact of waist circumference on the incidence of NAFLD in children. NAFLD, nonalcoholic fatty liver disease; CI, confidence interval.

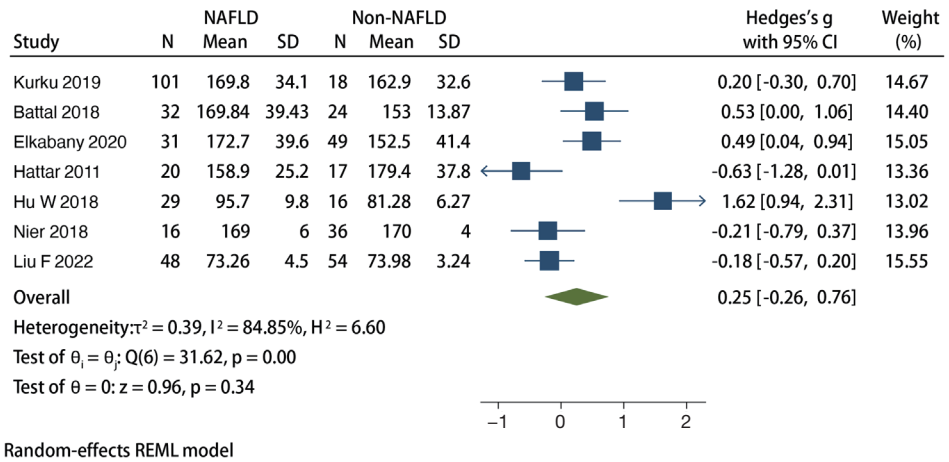

Figure 6 Forest plot of the effect of total cholesterol on the incidence of NAFLD in children. NAFLD, nonalcoholic fatty liver disease; CI, confidence interval.

were: I^2=84.85%, P<0.001, and thus the random-effects model was used for meta-analysis. The results showed that there was no statistically significant difference in total cholesterol between children with NAFLD and healthy children (MD =0.25 mg/dL, 95% CI: −0.26 to 0.76 mg/dL; *Figure 6*). Sensitivity analysis showed that deleting studies 1 by 1 would not significantly change the size of the overall effect, and the results were relatively stable.

Effect of triglyceride level on the development of NAFLD in children

The results of the heterogeneity test of the included studies were: I^2=95.68%, P<0.001, and thus the random-effects model was used for meta-analysis. The results showed that the triglyceride level in the NAFLD group was significantly higher than that in the control group (MD =1.08 mg/dL, 95% CI: 0.05 to 2.12 mg/dL; *Figure 7*). Sensitivity analysis showed that deleting studies 1 by 1 would not significantly change the size of the overall effect, and the results were relatively stable.

Effect of LDL level on the incidence of NAFLD in children

The results of the heterogeneity test of the included studies were: I^2=62.32 %, P=0.04, and thus the random-effects model was used for meta-analysis. The results showed

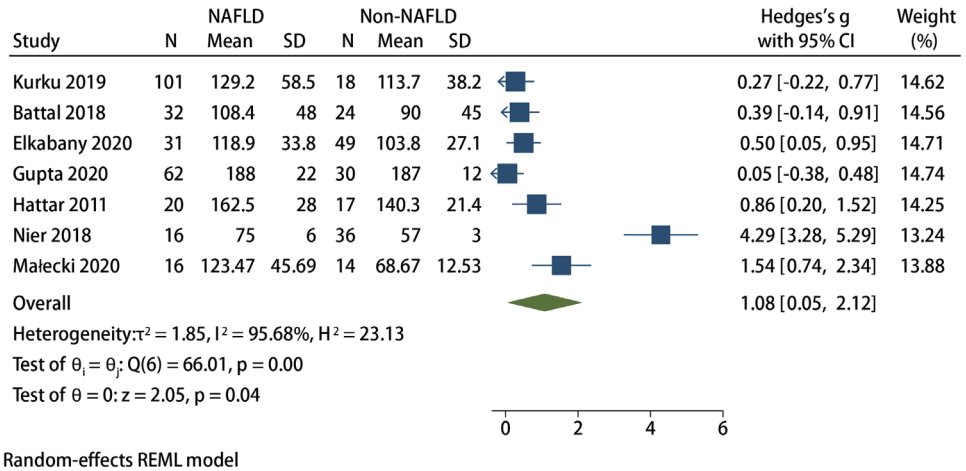

Figure 7 Forest plot of the effect of triglyceride level on the incidence of NAFLD in children. NAFLD, nonalcoholic fatty liver disease; CI, confidence interval.

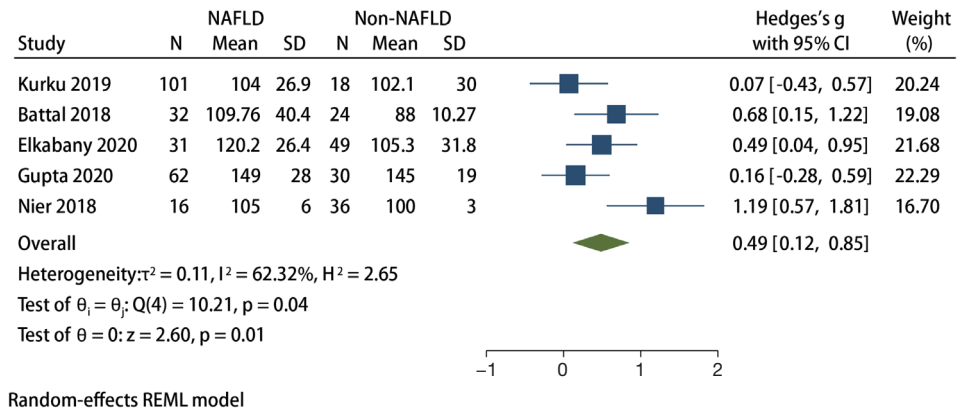

Figure 8 Forest plot of the effect of LDL level on the incidence of NAFLD in children. LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; CI, confidence interval.

that the LDL level in the NAFLD group was significantly higher than that in the control group (MD =0.49 mg/dL, 95% CI: 0.12 to 0.85 mg/dL; *Figure 8*). Sensitivity analysis showed that deleting studies 1 by 1 would not significantly change the size of the overall effect, and the results were relatively stable.

Effect of HDL level on the incidence of NAFLD in children

The results of the heterogeneity test of the included studies were: I^2=98.12%, P<0.001, and thus the random-effects model was used for meta-analysis. The results showed that there was no statistical difference in the HDL level of the NAFLD group compared with the healthy children (MD =−0.61 mg/dL, 95% CI: −2.25 to 1.03 mg/dL; *Figure 9*). Sensitivity analysis showed that deleting studies 1 by 1 would not significantly change the size of the overall effect, and the results were relatively stable.

Effect of fasting blood glucose on the development of NAFLD in children

The results of the heterogeneity test of the included studies were: I^2=18.92%, P=0.3, and thus the fixed-effect model was used for meta-analysis. The results showed that compared with healthy children, the fasting blood glucose in the NAFLD group was significantly higher than that in the control group

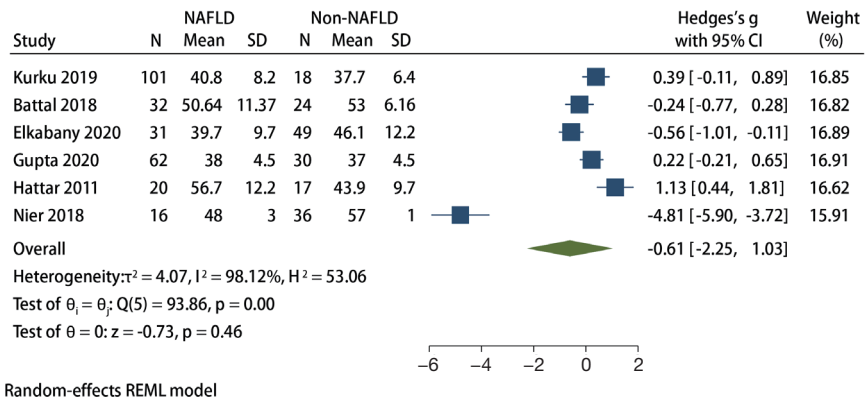

Figure 9 Forest plot of the effect of HDL level on the incidence of NAFLD in children. HDL, high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; CI, confidence interval.

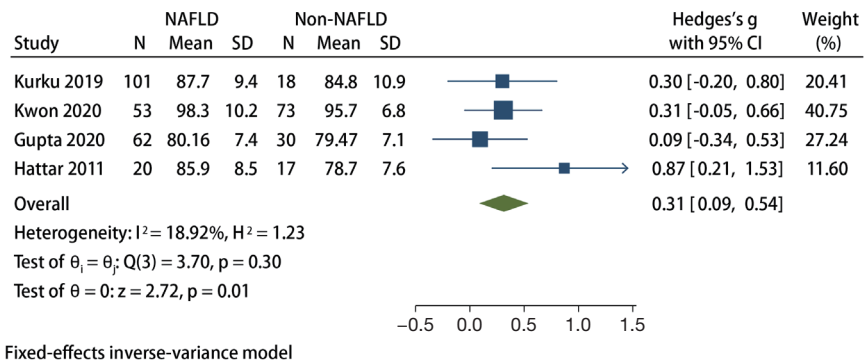

Figure 10 Forest plot of the effect of fasting blood glucose on the onset of NAFLD in children. NAFLD, nonalcoholic fatty liver disease; CI, confidence interval.

(MD =0.31 mg/dL, 95% CI: 0.09 to 0.54 mg/dL; *Figure 10*). Sensitivity analysis showed that deleting studies 1 by 1 would not significantly change the size of the overall effect, and the results were relatively stable.

Effect of insulin resistance index (HOMA-IR) on the incidence of NAFLD in children

The results of the heterogeneity test of the included studies were: I^2=96.59%, P<0.001, and thus the random-effects model was used for meta-analysis. The results showed that the insulin resistance index (HOMA-IR) of the NAFLD group was significantly higher than that of the control group (MD =2.95, 95% CI: 1.41 to 4.49; *Figure 11*). Sensitivity analysis showed that deleting studies 1 by 1 would not significantly change the size of the overall effect, and the results were relatively stable.

The effect of exercise on children with NAFLD (grade 0–3)

The effect size and standard error of the included studies were calculated by ordinal logistic regression (*Table 3*). The results of the heterogeneity test of the included studies were: I^2=0%, P=0.66, and thus the fixed-effect model was used for meta-analysis. The results showed that exercise had a significant effect on improving the degree of NAFLD in children (OR =2.51, 95% CI: 1.83 to 3.43; *Figure 12*). Sensitivity analysis showed that deleting studies 1 by 1 would not significantly change the size of the overall effect, and the results were relatively stable.

Publication bias

The funnel plot showed a slight asymmetry (*Figures 13-16*),

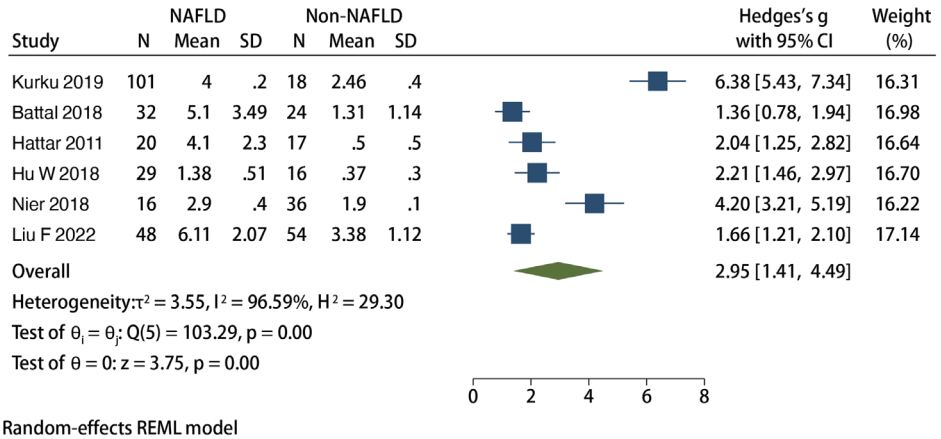

Figure 11 Forest plot of the impact of insulin resistance index (HOMA-IR) on the incidence of NAFLD in children. HOMA-IR, homeostasis model assessment of insulin resistance; NAFLD, nonalcoholic fatty liver disease; CI, confidence interval.

Table 3 Calculation results of the effect size and standard error of the included studies

Included studies	Effect size	Standard error
Antunes, 2013	0.563	0.592
Grønbæk H, 2012	0.694	0.279
Grønbæk H, 2012	0.847	0.344
Verduci, 2013	1.183	0.46
Koot BG, 2011	1.238	0.313

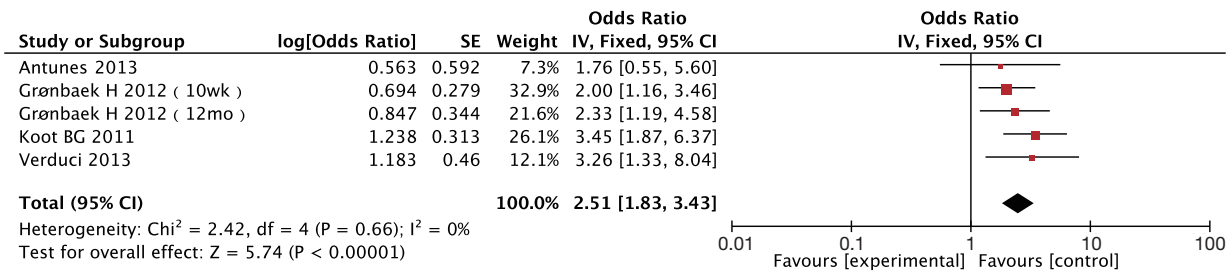

Figure 12 Forest plot of the effect of exercise on nonalcoholic fatty liver disease (0–3 degrees) in children. CI, confidence interval.

and we speculated that there may have been some publication bias, but it was difficult to quantify. However, when we used Begg's method to assess publication bias, we found that publication bias was not significant: $P_{(BMI)}$=0.4524, $P_{(waist\ circumference)}$=0.1329, $P_{(triglycerides)}$=0.0163, and $P_{(insulin\ resistance\ index)}$=0.1329.

Discussion

With rapid economic development and changes in lifestyle, the incidence of overweight and obese children worldwide is increasing at an alarming rate (1-3). This has become an increasingly serious public health problem that is endangering children's health. As of 2016, the overall prevalence of childhood obesity had reached 18.5% (28). Obesity seriously affects children's quality of life and physical and mental health and is also a high-risk factor for many chronic diseases. Childhood obesity has a higher probability of persisting into adulthood, potentially resulting in associated chronic conditions, such

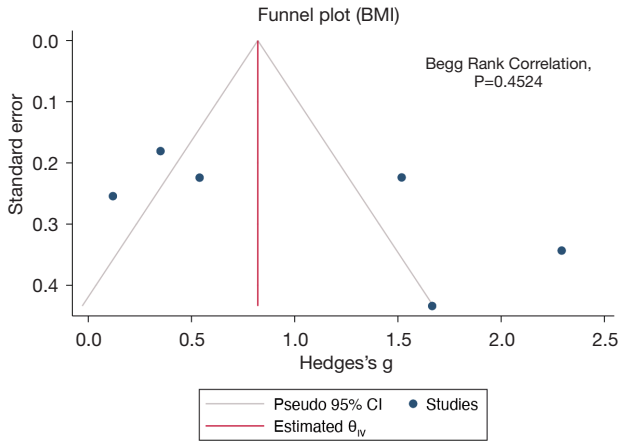

Figure 13 Funnel plot for BMI. BMI, body mass index.

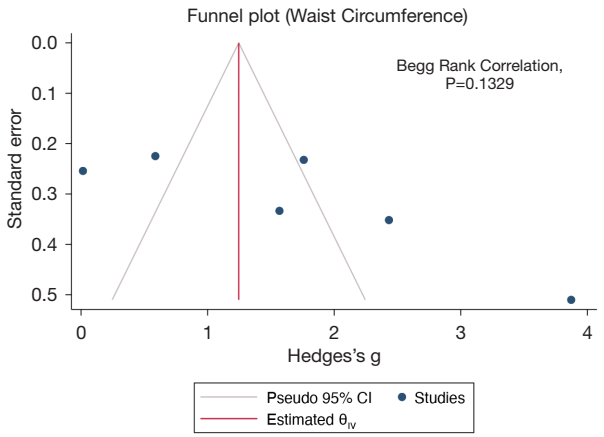

Figure 14 Funnel plot for waist circumference.

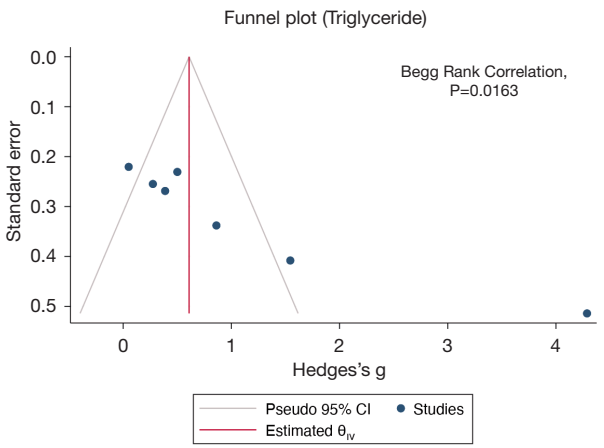

Figure 15 Funnel plot for triglycerides.

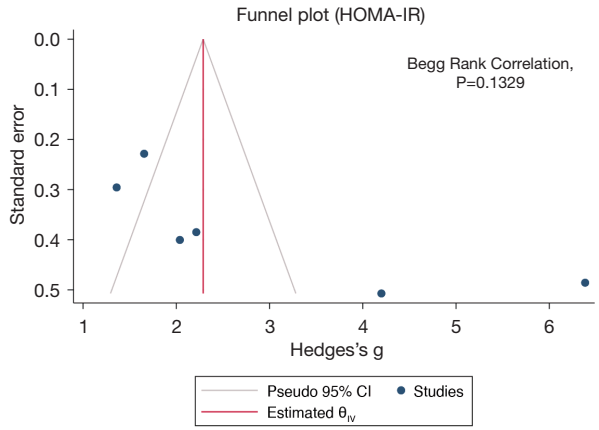

Figure 16 Funnel plot for insulin resistance index (HOMA-IR). HOMA-IR, homeostasis model assessment of insulin resistance.

as diabetes, hypertension, high cholesterol, atherosclerosis, cardiovascular and cerebrovascular diseases, and the development of specific tumors. Additionally, psychological and behavioral disorders may also arise (3,29).

NAFLD refers to a clinicopathological syndrome characterized by excessive fat deposition in liver cells not caused by alcohol or other definite liver damage factors (10) and is associated with insulin resistance and genetic susceptibility. NAFLD is the most common liver disease worldwide and a leading cause of liver-related morbidity and mortality (30). It is now also considered a hepatic manifestation of metabolic syndrome, and experts in the field have recently proposed a new, more representative term, "metabolic-associated fatty liver disease" (MAFLD) (30). NAFLD is the most common liver disease in children (31), usually occurring in the presence of metabolic syndrome and/or obesity in children, while genetic predisposition appears to be associated with more rapid progression, diabetes development, and increased cardiovascular risk. In addition, NAFLD is closely related to increased chances of liver transplantation (6,11,31). Therefore, with the increasing rate of childhood obesity, further control of the incidence of NAFLD in children is urgently needed.

Childhood obesity is known to be an important cause of the progressively increasing incidence of NAFLD in children (30). Although a large number of studies have reported the relationship between obesity and NAFLD in children (30-32), scientifically sound screening methods for NAFLD in obese children are still lacking. Therefore, this meta-analysis collected relevant data from children with

NAFLD and healthy children to investigate the differences in anthropometric and biochemical characteristics between children with NAFLD and healthy controls. We determined the obesity-related body parameters (height, weight, BMI, and waist circumference), lipid metabolism parameters (total cholesterol, triglycerides, HDL, and LDL), and glucose metabolism parameters (fasting blood sugar and insulin resistance index) associated with the incidence of NAFLD in children to enable the development of a standard screening method for the early detection, diagnosis, and treatment of the disease in our daily clinical work in pediatrics and provide a solid foundation for the establishment of its screening and diagnostic criteria. In addition, this study further evaluated the effect of exercise on NAFLD in children, providing new insights for controlling the incidence of NAFLD in children.

The results of the meta-analysis showed that BMI and waist circumference (WC) were significantly correlated with the presence of NAFLD in children, and higher BMI and WC values indicated a higher possibility of NAFLD in children. This was consistent with existing research findings. A study (33) from China that used a restricted cubic spline model to explore the dose-response relationship between continuous changes in BMI and fatty liver disease showed that regardless of sex (male/female), age after stratification (<50/≥50 years old), and the prevalence of hypertension (yes/no), the dose-response relationship between BMI and fatty liver disease was J-shaped (nonlinear test, P<0.001). Other study on children with NAFLD (32) has shown that WC, BMI, and the severity of fatty liver are closely related. WC has a stronger predictive power than BMI and is relatively simple to determine. Therefore, an important measure for preventing and reducing the occurrence of fatty liver in children is to control increases in WC and BMI.

The results of this meta-analysis showed that among obesity-related lipid metabolism data, triglyceride content and LDL were significantly associated with the presence of NAFLD in children, suggesting a higher incidence of NAFLD in children. Triglyceride is a type of fat found in the blood that is mainly metabolized by the liver. If triglycerides continue to increase and exceed the metabolic capacity of the liver, excessive fat will accumulate in the liver, and in the long run, cause fatty liver (34). At the same time, the liver function of patients with fatty liver has been damaged, and the ability to metabolize fat has decreased, resulting in the deposition of large amounts of lipids in the liver and blood circulation, which will increase triglycerides in the blood (34). Therefore, high blood triglyceride levels are likely to cause fatty changes in the liver, thereby increasing the incidence of NAFLD (35). LDL is a lipoprotein particle that carries cholesterol into peripheral tissue cells and can become oxidized (36). When the amount of LDL, especially oxidized LDL (OX-LDL) is excessive, the cholesterol it carries accumulates in the liver, leading to the development of hepatic steatosis (34). However, in our study, a correlation between total cholesterol (TC) and NAFLD in children was not observed, although studies of adult patients with NAFLD (36,37) have shown that increased TC is a risk factor for the development of NAFLD in adults. For instance, an analysis examining the relationship between fatty liver and blood sugar, blood lipids, and liver function in a random population of patients undergoing physical examinations (38) revealed that serum total cholesterol (TC) levels increased as fatty liver worsened, indicating a correlation between the two. We hypothesize that the main reasons for the discrepancy with the findings of this study are: (I) our study population consists of children, and there are substantial differences in various parameters between adults and children; (II) the ratio of male to female participants varied significantly among the studies included in this analysis; and (III) the research papers incorporated in our study originated from different countries, potentially leading to considerable variations in the samples.

The results of this study showed that among obesity-related indicators, glucose metabolism, fasting glucose, and insulin resistance index (HOMA-IR) were significantly correlated with the presence of NAFLD in children. Previous studies have reported that as the adipose tissue of patients with fatty liver has insulin deficiency or insulin resistance, the surrounding fat breaks down and releases large quantities of free fatty acids and triglycerides, further depositing fat in the liver (39). Therefore, parameters related to glucose metabolism (fasting blood glucose and insulin resistance index, etc.) are also sensitive indicators for early screening and diagnosis of NAFLD in children.

In addition, this study found that exercise could significantly improve the disease process of children with NAFLD and effectively improve the degree of NAFLD in children. A recent study reported that there is no specific drug for the treatment of NAFLD in children, only exercise and dietary intervention (40). Therefore, we concluded from the results of this meta-analysis that the first step in the treatment of NAFLD in children is to prevent obesity and stimulate lifestyle changes through physical activity and a healthier diet. Another study (41) found that physical

exercise, even without weight loss, seemed to reduce the degree of steatosis. Exercise alone, lifestyle changes through a healthier diet, gradual weight loss, and increased physical activity appear to be the only effective treatments for the disease at present.

However, there are certain limitations in this study. In including Chinese research literature, this study only searched against the China National Knowledge Infrastructure (CNKI) database and did not extend the scope to other databases, such as Wanfang medical database, which may result in the retrieved Chinese studies not being comprehensive. Moreover, the heterogeneity of the studies included in this study is high. This may be related to the following factors: (I) the underlying disease characteristics of the population included in the study are different, which may have an impact on the accuracy of the research results. (II) the diagnostic criteria for nonalcoholic fatty liver disease may vary among the studies included. (III) differences in the proportion of male and female subjects included in these studies may also lead to biased results. (IV) the included literature comes from different countries, and the sample may vary.

Conclusions

In summary, this study found that various physical indicators related to obesity have certain predictive effects for children with NAFLD: BMI, WC, triglyceride content, LDL, fasting blood glucose, and insulin resistance index (HOMA-IR) were all significantly correlated with children with NAFLD. In addition, exercise could significantly improve the degree of steatosis in children with NAFLD. Therefore, in the clinical work of pediatrics, the above indicators could be monitored for early prevention, prediction, and diagnosis of NAFLD in children. In addition, effective treatment of NAFLD in children through exercise therapy could be conducted in a timely manner.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-123/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-123/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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