

Efficacy of probiotics on nonalcoholic fatty liver disease

A meta-analysis

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Abstract

Objectives: The intestinal flora is closely related to the pathogenesis of nonalcoholic fatty liver disease (NAFLD). This study intends to systematically evaluate the efficacy and safety of probiotics in the treatment of NAFLD through a meta-analysis of published randomized controlled trials.

Methods: This study was conducted through a search of published randomized controlled trials using probiotic-related drugs for the treatment of nonalcoholic fatty liver disease (up to April 6, 2022). The JADAD evaluation table was used to evaluate the quality of the literatures included in the search, and the risk of bias was evaluated according to the Cochrane evaluation manual. Finally, RevMan5.4 software was used for meta-analysis.

Results: A total of 21 randomized clinical trials involving 1037 patients with NAFLD were included in this study. Meta-analysis results showed that after probiotic intervention, liver function, blood lipid level, blood glucose levels and insulin levels were significantly reduced, which had a good effect on improving hepatic steatosis. However, it did not significantly improve BMI, inflammatory factors, or homeostasis model assessment of insulin resistance. Through the subgroup analysis of the course of treatment, it was found that ALT, GGT, TG, and blood sugar improved better in the probiotic treatment course of greater than or equal to 12 weeks.

Conclusion: This study shows that the use of probiotics therapy has a good regulating effect on liver function, steatosis, blood glucose level, insulin level and blood lipid level in NAFLD patients.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GGT = glutamyl transpeptidase, h-CRP = C-reactive protein, IL-6 = interleukin-6, LPS = lipopolysaccharides, NAFLD = nonalcoholic fatty liver disease, TC = total cholesterol, TG = triglyceride, TNF- α = tumor necrosis factor- α .

Keywords: efficacy, meta-analysis, nonalcoholic fatty liver disease (NAFLD), probiotics, safety

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a common chronic liver disease that is usually caused by nonalcoholic or drug-induced fatty deposition in the liver and hepatocyte steatosis,^[1] with a global incidence of about 25%.^[2] The onset of nonalcoholic liver disease is insidious, with no obvious symptoms in the initial stage. If there is no timely intervention, it can progress to nonalcoholic steatohepatitis, nonalcoholic liver fibrosis, and even liver cirrhosis and liver cancer in the later stage.^[3] In addition, nonalcoholic fatty liver disease (NAFLD) is also the main cause of liver disease in children.^[4] With the change of social lifestyle, the number of patients is increasing, which has caused a serious burden on public health.

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The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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*Correspondence: Sufang Zhou, The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Guiyang 550001, China (e-mail: zhsfang2669@126.com). The pathogenesis of NAFLD is complex. According to the "multiple blows" theory, it is believed that abnormal fat metabolism and the production of inflammatory factors are important factors in the occurrence and development of NAFLD.^[5] And then, obesity, cardiovascular and cerebrovascular diseases, type 2 diabetes, and intestinal microbes are all risk factors for the induction of nonalcoholic fatty liver disease.^[6] Currently, many studies have found that gut microbiota plays an important role in regulating obesity, improving fat metabolism, and reducing inflammation. Some studies have found that NAFLD could improve and be repaired by FMT or probiotic intervention.^[7–9] When the intestinal flora is dysregulated, lipopolysaccharide is released, activates TLR-related receptors,^[10] and participates

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and reduce inflammation by regulating the balance of intestinal

flora.^[18,19] Therefore, probiotics are used as a potential therapy

in the clinical treatment of nonalcoholic fatty liver disease. Its safety and efficacy remain controversial. This study systemat-

ically reviewed the relevant literature on the use of probiotic

therapy in the treatment of nonalcoholic liver disease in recent

years and analyzed the probiotic therapy from the aspects of

liver function, blood sugar level, insulin level, insulin resistance,

lipid and lipid metabolism, and inflammatory factors, and non-

alcoholic liver efficacy and safety.

in the mechanism of insulin resistance.^[11,12] At the same time, lipopolysaccharides (LPS) enters the liver through the hepatic portal vein, is recognized by kupffer, and activates the NF-K β inflammatory signaling pathway to produce a large number of inflammatory factors, such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), etc.^[13,14] At present, the main treatment and intervention measures for NAFLD are lifestyle intervention and weight loss,^[15] and effective and unified targeted therapy drugs are still in the research and development stage.^[16,17] Recent studies have shown that probiotics can improve fat metabolism

Table

Basic chara	cteristics of	of included studies.							
Included studies	Date of publication	Age C/T	Region	Number of cases C/T	Treatment measures in the observation group	Treatment measures in the observation group	Course of treatment, wk	Included outcome observations	Method of diagnosis
Ahn ^[21]	2019	41.7±12.49/42.06±2.18	Italy	35/30	Probiotic	Placebo	12	1.2.4.5.6.7.8.9.10.11.12.13.15.16	MRI
A 11 1/00]			<u> </u>		mixture		10		
Alisi ^[22] Aller ^[23]	2014 2011	11±2/10±2 44.3±15.1/49.4±10.9	Spain Iran	22/22 14/14	VSL#3 Lactobacillus bulgaricus and strep- tococcus thermoph- ilus	Placebo Placebo	16 12	1.5.10.15.17 1.2.3.4.6.7.8.9.10.11.12.15.16	Hepatic biopsy Hepatic biopsy
Asgharian ^[24]	2016	46.57±1.7/47.78±1.7	Iran	38/36	Probiotic mixture	Placebo	8	1.2.14.15.17.18	Ultrasound
Behrouz ^[25]	2020	$38.43 \pm 10.09/38.46 \pm 7.11$		29/30	Probiotic	Placebo	12	1.2.4.5.6.7.8.14.15	Ultrasound
Bomhof ^[26]	2018	20-60/20-60	Britain	5/8	Oligofructose	Placebo	12	1.2.3.4.6.8.9.10.11.12.13.15.16	Hepatic biopsy
Chong ^[27]	2021	$58 \pm 7/57 \pm 8$	India	16/19	VSL#3	Placebo	10	1.2.4.6.7.10.14.18	Hepatic biopsy
Duseja ⁽²⁸⁾	2019	33±6/38±10	Iran	20/19	High potency multistrain probiotic prepara- tion	Placebo	48	1.2.11.12.13.15.17.18	Hepatic biopsy
Ekhlasi ^[29]	2016	25-64/25-64	Iran	15/15	Symbiotic capsule	Placebo	8	1.2.4.5.8.9.10.15.18	Ultrasound
Eslamparast ^[30]	2014	46.35±8.8/45.69±9.5	Iran	26/26	Synbiotic supple- mentation	Placebo	28	1.2.3.8.10.12.14.15.18	Hepatic biopsy
Famouri ^[31]	2016	12.6±1.7/12.7±2.2	Italy	32/32	Probiotic capsule	Placebo	12	1.2.4.6.7.17	Ultrasound and liver function
Javadi ^[32]	2017	$42.21 \pm 9.11/43.90 \pm 9.02$	Iran	20/19	Probiotic capsule	Placebo	8	1.2.3.15	Ultrasound and liver function
Kobyliak ^[33]	2018	57.29±10.45/53.4±9.55	Ukraine	20/30	Symbiter	Placebo	8	1.2.3.4.5.6.7.11.12	Ultrasound
Kobyliak ^[34]	2018	53.91±11.45/53.92±9.42	Ukraine	22/26	Probiot- ic-omega	Placebo	8	1.2.4.5.6.7.11.12	Ultrasound
Kobyliak ^[35]	2019	57.38±9.92/53.23±10.09	Ukraine	24/26	Symbiter forte	Placebo	8	1.2.3.4.5.6.7.11.12	Ultrasound
Manzhalii ^[36]	2017	$43.5 \pm 1.3/44.3 \pm 1.5$	Ukraine	37/38	LBSF	Placebo	12	1.2.3.4.5.8.15.18	Ultrasound
Nabavi ^[37]	2014	44.05±8.14/42.75±8.72	Iran	36/36	Probiotic yogurt	Conventional yogurt	8	1.2.4.5.6.7.8.15.17	Ultrasound
Scorletti ^[38]	2020	$51.6 \pm 13.1/50.2 \pm 12.4$	Den- mark	44/45	Prebiotic	Placebo	40–56	1.2.3.4.5.6.7.8.9.13.15	MRS
Shavakhi ^[39]	2013	$46.9 \pm 5.2/46.9 \pm 5.2$	Iran	32/31	Protexin + metformin	Placebo + Metformin	24	1.2.4.5.8.15.17.18	Hepatic biopsy
Vajro ^[40]	2011	10.7±2.1/10.7±2.1	Italy	10/10	Lactobacillus GG	Placebo	8	1.12.18	Ultrasound and liver function
Wong ^[41]	2013	$42 \pm 9/55 \pm 9$	Britain	10/10	Lactobacillus- delrueckii	Usual care	24	1.2.4.5.6.7.8.15.18	Hepatic biopsy

1. ALT, 2. AST, 3. GGT, 4. TC, 5. TG, 6. HDL-C, 7. LDL-C, 8. Glucose level, 9. Insulin level, 10. Insulin resistance, 11. IL-6, 12. TNF-α, 13. LPS, 14. h-CRP, 15. BMI, 16. Total fat content, 17. Grading of steatosis 18 Adverse reactions

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GGT = glutamyl transpeptidase, h-CRP = C-reactive protein, IL-6 = interleukin-6, LPS = lipopolysaccharides, TC = total cholesterol, TG = triglyceride, TNF- α = tumor necrosis factor- α .

2. Methods

2.1. Search strategy and study selection

In this study, we searched literature databases such as EMbase, PubMed, Web of Science, Cochrane, etc., using the combination of subject headings and free words. Search terms included: Nonalcoholic Fatty Liver Disease, Gastrointestinal Microbiome, Probiotic, randomized controlled trial, etc. The retrieval time is from the establishment of the retrieval database to April 6, 2022.

2.2. Literature inclusion and exclusion criteria

The inclusion criteria of the study were as follows: a randomized controlled study using probiotics as an intervention method, and the control group is a placebo; confirmed by imaging examination (such as ultrasound, CT, MRI, liver elastography, etc.) or histological examination nonalcoholic fatty liver disease; Outcome indicators include at least changes from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and body mass index (BMI); Studies written in English or Chinese. All included studies were not limited by age, gender, race, disease duration, and geographical location.

Literature exclusion criteria were as follows: hepatic steatosis induced by other causes, such as alcoholic hepatitis, viral hepatitis, hereditary hepatitis, etc.; the outcome indicators cannot be completely obtained (e.g., some outcome indicators are not reported using the mean and variance, which cannot be reviews, animal studies, case reports, conference abstracts, etc.; and duplicate literature, non-randomized controlled trials. A total of 21 studies that met the criteria were finally included in the meta-analysis.

2.3. Data extraction and quality assessment

Two researchers independently screened the literature. According to the inclusion and exclusion criteria, the titles and abstracts of the literatures were preliminarily read, and the literatures that did not meet the criteria were eliminated. After further reading the full text, the studies for inclusion were finally selected. If there was any disagreement during the screening process, it was assessed by a third-party researcher, and the disagreement would be resolved through negotiation. Extracted data included authors, publication time, region, intervention measures, duration of intervention, patient age, number of cases, and outcome

Table 2

Included research methodology JADAD quality evaluation.

Author	Date of publication	Randomized sequence generation	Randomize hide	Blind	Withdrawal and loss to follow-up	Total score	Literature quality
Ahn	2019	Y2	Y2	Y2	N1	7	High
Alisi	2014	Y2	Y2	Y2	N1	7	High
Aller	2011	Y2	Y2	Y2	N1	7	High
Asgharian	2016	Y2	Y2	Y2	N1	7	High
Behrouz	2020	Y2	Y2	Y2	N1	7	High
Bomhof	2018	Y2	Y2	Y2	N1	7	High
Chong	2021	Y2	Y2	Y2	N1	7	High
Duseja	2019	Y2	Y2	Y2	N1	7	High
Ekhlasi	2016	Y2	Y2	Y2	N1	7	High
Eslamparast	2014	Y2	Y2	Y2	N1	7	High
Famouri	2016	Y2	Y2	Y2	N1	7	High
Javadi	2017	Y2	Y2	Y2	N1	7	High
Kobyliak	2018	Y2	Y2	Y2	N1	7	High
Kobyliak	2019	Y2	Y2	NO	N1	5	High
Kobyliak	2018	Y2	Y2	Y2	N1	7	High
Manzhalii	2017	Y2	Y2	Y 2	N 1	7	High
Nabavi	2014	Y2	Y2	Y1	N1	6	High
Scorletti	2020	Y2	Y2	Y 2	N 1	7	High
Shavakhi	2013	Y2	Y2	Y1	N1	6	High
Vajro	2011	Y2	Y2	Y2	N1	7	High
Wong	2013	Y2	NO	NO	Y1	3	Lower

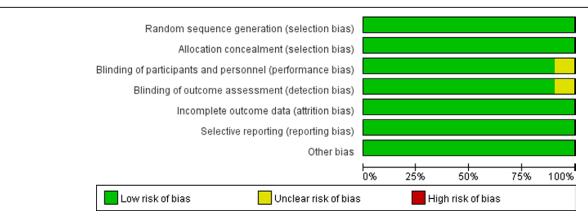


Figure 1. Risk of bias graph. A total of 21 studies that met the criteria were finally included in the meta-analysis. Three of the study participants were children, and one of the study participants had coexisting type 2 diabetes; two of the studies were not explicitly blinded, and one study was not randomized concealed.

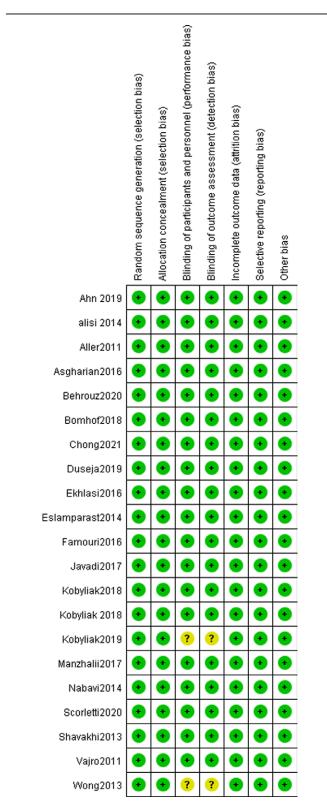


Figure 2. Risk of bias summary. A total of 21 studies that met the criteria were finally included in the meta-analysis. Three of the study participants were children, and one of the study participants had coexisting type 2 diabetes; two of the studies were not explicitly blinded, and one study was not randomized concealed.

indicators. The outcome indicators were expressed as mean \pm standard deviation, and the literature data was recorded in EXCEL form. If it could not be directly extracted, it was extracted according to the original data recorded in the original

literature, and the indicators of different units were converted into the study after equal conversion. The basic characteristics of the research literature included in the meta-analysis are shown in Table 1.

The quality of the literature included in the included studies was assessed by the JADAD rating scale, and articles with a score of <3 were excluded (Table 2). The risk of bias assessment was independently assessed by two researchers using the Cochrane Evaluation Manual (Figs. 1 and 2).^[20]

2.4. Outcome indicators and data analysis

In this study, liver function and steatosis classification were used as the main outcome indicators, and secondary indicators included blood lipid levels, blood glucose levels, insulin levels, insulin resistance, inflammatory factors, and BMI.

All data were analyzed using RevMan 5.4 software. Enumeration data were expressed as relative risk (RR) and its 95% confidence interval (CI), and measurement data were expressed as mean difference (MD) and its 95% CI, with a P value less than 0.05 The results were statistically significant. The heterogeneity among the results of the included studies was quantified by I^2 . If there is no statistical heterogeneity (I^2 < 50%) among the results of each study, a fixed effect model is used for meta-analysis; if there is statistical heterogeneity $(I^2 >$ 50%) among the results of each study, further analysis of heterogeneity is performed After excluding the influence of obvious clinical heterogeneity, a random-effects model was used for meta-analysis. Significant clinical heterogeneity was addressed using methods such as subgroup analysis or sensitivity analysis, or by descriptive analysis. All results are represented by forest plots. This study was approved by the by the ethical review committee of Guizhou University of Traditional Chinese Medicine.

3. Results

3.1. Search results

The process of literature search, evaluation, exclusion, and inclusion is shown in Figure 3. A total of 21 research reports were finally included, involving 1037 participants. Three of the study participants were children, and one of the study participants had coexisting type 2 diabetes; two of the studies were not explicitly blinded, and one study was not randomized and concealed.

3.2. Effects of probiotics on liver function levels

A total of 21 studies reported the mean change in ALT from baseline (Fig. 4A): the results of the analysis showed that ALT levels were significantly reduced after probiotic intervention, (MD = -8.52, 95% CI [-12.59, -4.46], P < .00001), the results were significantly different. A total of 18 studies reported the mean change from baseline in AST (Fig. 4B): the analysis showed that AST levels were significantly reduced after probiotic intervention, (MD = -6.82, 95% CI [-10.16, -3.49], P < .00001), the results were significantly different; a total of 10 studies reported the mean change from baseline in glutamyl transpeptidase (GGT) (Fig. 4C), and the analysis showed that GGT levels were significantly reduced after probiotic intervention, (MD = -5.88, 95% CI [-6.59, -5.16], P < .00001), the results are significantly different.

Due to the significant heterogeneity of the results (ALT $I^2 = 96\%$, AST $I^2 = 95\%$ GGT = $I^2 = 86\%$ P < .00001), we found that in the ALT study, excluding Ahn, Alisi, Aller, Duseja, Eslamparast, Javadi, Scorletti, Vajro, Wong and other research literatures, the heterogeneity was significantly reduced, $I^2 = 48\%$

P = .05, the analysis results showed: MD = -15.13, 95% CI [-19.41, -10.86]; In the AST study, after excluding Eslamparast, Manzhalii, Nabavi, Shavakhi, Wong and other studies, the heterogeneity was significantly reduced, $I^2 = 0\% P = .53$, the analysis results showed: (MD = -5.48 95% CI [-6.16, -4.81], P < .00001); in the GGT study, after excluding Bomhof, Eslamparast, Kobyliak and other studies, the heterogeneity was significantly reduced, $I^2 = 0\% P = .53$, the analysis results showed: (MD = -5.95, 95% CI [-7.00, -4.90], P < .00001). A review of the source literature with heterogeneity found nothing. And the meta-analysis results did not change significantly due to heterogeneity, so we considered that the source of heterogeneity was caused by differences in treatment courses and medication.

3.3. Effects of probiotics on the grading of hepatocyte steatosis

A total of 6 studies reported changes from baseline in steatosis (Fig. 5A–D): the results of the analysis showed that the degree of hepatic steatosis was significantly improved after the intervention with probiotic therapy, with steatosis grade 0 (MD = 3.05, 95% CI [1.86, 5.00], P < .00001); steatosis grade 1 (MD = 0.99, 95% CI [0.77, 1.27], P = .92); steatosis grade 2 (MD = 0.57, 95% CI [0.37, 0.88], P = .01); steatosis grade 3, (MD = 0.75, 95% CI [0.41, 1.39], P = .37). However, the results showed that only steatosis grades 0 and 2 were statistically significant.

Due to the significant difference in the results of grade 1 steatosis, $I^2 = 60\%$, we found that after excluding Duseja, Famouri and other studies, the heterogeneity was significantly reduced, $I^2 = 31\%$, P = .23, the analysis results It shows that: (MD = 1.21, 95% CI [0.91, 1.60], P = .19), reviewing the source literature of heterogeneity, nothing was found. And the meta-analysis results did not change significantly due to heterogeneity, so we considered that the source of heterogeneity was caused by differences in treatment courses and medication.

3.4. Effects of probiotics on total fat mass level and BMI

A total of 3 studies reported changes from baseline in total fat mass levels (Fig. 6A): the results of the analysis showed that

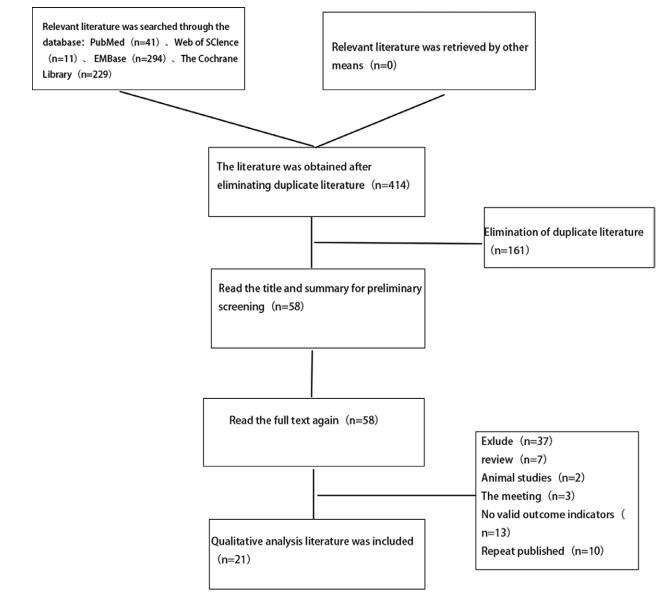


Figure 3. Flowchart of study selection. The process of literature search, evaluation, exclusion, and inclusion is shown in Figure 3. A total of 21 research reports were finally included, involving 1037 participants.

~		eriment			Control			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
Ahn 2019	38.8	35	30	44.5	23	35	3.6%	-5.70 [-20.36, 8.96]		
alisi 2014	33	1	22	50	5	22	6.8%	-17.00 [-19.13, -14.87]	•	
Aller2011	60.4	30.4	14	64.8	35.5	14	2.0%	-4.40 [-28.88, 20.08]		
Asgharian2016	26.88	4.28	36	35.07	4.35	38	6.8%	-8.19 [-10.16, -6.22]	•	
Behrouz2020	30	0.75	30	38	9.86	29	6.6%	-8.00 [-11.60, -4.40]	-	
Bomhof2018	68.1	14	8	59.3	14.2	5	3.4%	8.80 [-6.98, 24.58]		
Chong2021	51	32	19	49	26	16	2.7%	2.00 [-17.22, 21.22]		
Duseja2019	42.52	16.97	19	67.32	35.17	20	3.1%	-24.80 [-42.00, -7.60]		
Ekhlasi2016	31.59	9.42	15	38.05	6.54	15	6.1%	-6.46 [-12.26, -0.66]		
Eslamparast2014	44.2	3.8	26	64.17	11.1	26	6.4%	-19.97 [-24.48, -15.46]	+	
Famouri2016	26.2	12.9	32	23.1	9.6	32	6.1%	3.10 [-2.47, 8.67]	<u>+-</u>	
Javadi2017	40.3	12.74	19	50.42	14.12	20	5.3%	-10.12 [-18.55, -1.69]		
Kobyliak2018	37.04	7.58	30	39.75	2.11	28	6.7%	-2.71 [-5.53, 0.11]	-	
Kobyliak 2018	31.53	1.91	30	38.68	11.14	28	6.4%	-7.15 [-11.33, -2.97]	+	
Kobyliak2019	35.88	16.89	26	35.93	16.32	20	5.1%			
Manzhalii2017	35.88	2.2	38	35.93 50.4	3.1	37	5.1% 6.9%	-0.05 [-9.26, 9.16] -11.40 [-12.62, -10.18]		
Nabavi2014	25.5	2.1	36	24.5	1.64	36	6.9%	1.00 [0.13, 1.87]		
Scorletti2020	50.38	21.93	45	55.01	30.06	44	4.6%	-4.63 [-15.58, 6.32]		
Shavakhi2013	45.2	32.5	31	112.5	68.7	32	1.8%	-67.30 [-93.71, -40.89]		
Vajro2011	40.1	22.37	10	61.6	31.8	10	2.0%	-21.50 [-45.60, 2.60]		
Wong2013	46	61	10	94	34	10	0.8%	-48.00 [-91.28, -4.72]		
									•	
Total (95% CI)			526				100.0%	-8.52 [-12.57, -4.47]	•	
Heterogeneity: Tau ²	= 61.67; (Chi ^z = 51	14.82,	df = 20 ((P < 0.00	0001); I	²= 96%	ł	-100 -50 0 50 10	00
Test for overall effec	t: Z = 4.12	2 (P < 0.0	0001)							00
									Favours [experimental] Favours [control]	
_										
B										
	E		-1					Manu Difference	Mana Difference	
		eriment			Control			Mean Difference	Mean Difference	
Study or Subgroup	Mean		Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
Ahn 2019	32.5	22	30	31.7	28.5	35	3.7%	0.80 [-11.49, 13.09]		
Aller2011	35.6	10.4	14	36.4	13.8	14	4.8%	-0.80 [-9.85, 8.25]		
Asgharian2016	23.67	1.73	36	29.03	2.08	38	7.4%	-5.36 [-6.23, -4.49]	•	
Behrouz2020	30	5.75	30	38	15.25	29	6.0%	-8.00 [-13.92, -2.08]		
Chong2021	38	20	19	49	26	16	2.8%	-11.00 [-26.59, 4.59]		
Duseja2019	36	16.4	19	44.9	18.5	20	4.1%	-8.90 [-19.86, 2.06]		
Ekhlasi2016	30.52	10.4	15	34.54	6.8	15	6.9%	-4.02 [-7.50, -0.54]	-	
									_	
Eslamparast2014	35.1	2.7	26	60.34	13.1	26	6.3%	-25.24 [-30.38, -20.10]		
Famouri2016	24.3	7.7	32	26.6	11.8	32	6.4%	-2.30 [-7.18, 2.58]		
Javadi2017	31.15	9.08	19	41.63	12.46	20	5.7%	-10.48 [-17.30, -3.66]		
Kobyliak2018	32.98	8.39	30	41.3	6.45	28	6.8%	-8.32 [-12.16, -4.48]	+	
Kobyliak 2018	25.72	3.6	26	31.08	0.77	22	7.3%	-5.36 [-6.78, -3.94]	•	
Kobyliak2019	30	7.06	26	36.84	4.28	24	6.9%	-6.84 [-10.05, -3.63]	+	
Manzhalii2017	32.7	2.4	38	47.6	3.2	37	7.3%	-14.90 [-16.18, -13.62]	•	
Nabavi2014	27.5	5.62	36	25	0.41	36	7.3%	2.50 [0.66, 4.34]	+	
Scorletti2020	34	16.8	45	40.8	24	44	5.0%	-6.80 [-15.42, 1.82]		
Shavakhi2013	44.2	33.9	31	113.4	71	32	1.2%	-69.20 [-96.54, -41.86]		
Wong2013	44.2	55.5	10	113.4	17	10	4.1%			
wong2015	57	0	10	15	17	10	4.170	22.00 [10.83, 33.17]		
T-1-1 (054) (0)						470	400.00			
Total (95% CI)			482				100.0%	-6.82 [-10.16, -3.49]	· · · ·	
Heterogeneity: Tau ²				df = 17	(P < 0.1	00001)	l² = 95%		-100 -50 0 50	100
Test for overall effec	t: Z = 4.0'	1 (P < 0.	0001)						Favours (experimental) Favours (control)	
									Favours [experimental] Favours [control]	
<u>^</u>										
	Expe	rimenta	al	C	ontrol			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Aller2011	107.7	60.8	14	83.6	65.3	14	0.3%	24.10 [-22.64, 70.84]		
Behrouz2020	33	15	30	39	14.25	29	7.5%	-6.00 [-13.46, 1.46]		
Bomhof2018	62.3	14.9	8	44.7	7.2	5	3.8%	17.60 [5.50, 29.70]		
			-							
Eslamparast2014	74.42	1.8	26	83.78	3.1	26	17.5%	-9.36 [-10.74, -7.98]	-	
Javadi2017	35.75	16.35	19	35.89	21.77	20	3.9%	-0.14 [-12.18, 11.90]		
Kobyliak2018	41.13	5.3	30	46.26	4.44	28	15.8%	-5.13 [-7.64, -2.62]	•	
Kobyliak 2018	41.78	6.02	26	49.23	4.8	22	14.7%	-7.45 [-10.51, -4.39]	*	
Kobyliak2019	41.65	3.04	26	44.1	1.94	24	17.4%	-2.45 [-3.85, -1.05]	•	
Manzhalii2017	46.8	2.6	38	52.8	3	37	17.6%	-6.00 [-7.27, -4.73]	•	
Scorletti2020	40.0	36	45	42	61	44	1.5%	-2.00 [-22.87, 18.87]		
5001101112020	40	30	40	42	01	44	1.0 %	2.00 [22.07, 10.07]		
Total (95% CI)			262			240	100.0%	-4.76 [-7.42, -2.09]	▲	
				- 0.7				-4.70[-7.42, -2.09]		
	40.40.0									
Heterogeneity: Tau ² =				= 9 (P -	< 0.000i	01),1 -	00 %		-100 -50 0 50	100
Heterogeneity: Tau ² = Test for overall effect:				= 9 (P ·	< 0.000i	01),1 -	00 %	-	-100 -50 0 50	10

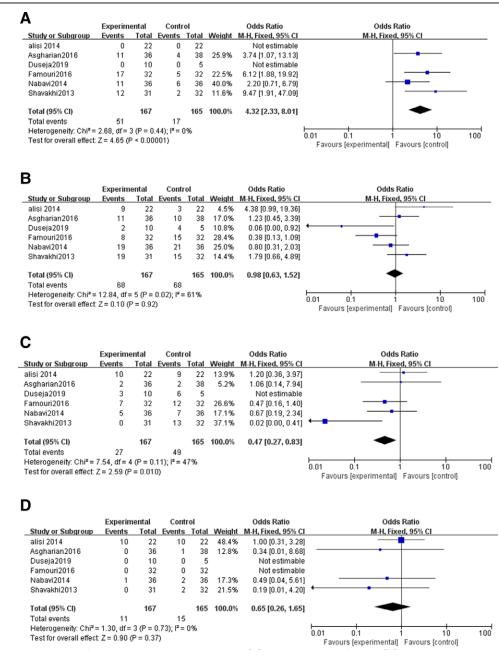
Figure 4. The Liver Function Levels. A total of 21 studies reported the mean change in ALT from baseline (A): the results of the analysis showed that ALT levels were significantly reduced after probiotic intervention, A total of 18 studies reported the mean change from baseline in AST (B): the analysis showed that AST levels were significantly reduced after probiotic intervention. the results were significantly different; a total of 10 studies reported the mean change from baseline in GGT (C). ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = glutamyl transpeptidase.

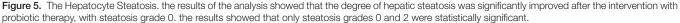
after probiotic intervention, total fat content was reduced, (MD = -1.20, 95% CI [-3.29, 0.88], *P* = .26). But the results were not statistically significant. A total of 15 studies reported changes in BMI from baseline (Fig. 6B): the analysis showed that BMI was significantly reduced after probiotic intervention, (MD = -1.69, 95% CI [-1.90, -1.49], *P* < .00001).

Due to the significant difference in BMI results, $I^2 = 94\%$, we found that after excluding Ahn, Manzhalii, Shavakhi, Wong and other studies, the heterogeneity was significantly reduced, $I^2 = 38\%$, P = .10, analysis. The results showed that: (MD = -0.11, 95% CI [-0.51, 0.29], P = .60), the Meta-analysis results changed significantly.

3.5. Effects of probiotics on blood glucose and insulin levels

A total of 11 studies reported changes in blood glucose from baseline (Fig. 7A): the analysis showed that blood glucose levels decreased after probiotic intervention, (MD = -0.27, 95% CI [-0.48, -0.06], P = .01). A total of 5 studies reported changes in insulin from baseline (Fig. 7B): the analysis showed that after probiotic intervention, insulin levels decreased, (MD = -0.72, 95% CI [-1.14, -0.30], P = .0008). A total of 7 studies reported changes from baseline in insulin resistance (Fig. 7C): the analysis showed that insulin resistance was reduced after probiotic intervention, (MD = 0.19, 95% CI [-0.44, 0.06], P = .14).





Due to the significant difference in blood glucose results, $I^2 = 64\%$, we found that after excluding the studies of Bomhof and others, the heterogeneity was significantly reduced, $I^2 = 1\%$, P = .43, the analysis results showed: (MD = -0.13, 95% CI [-0.23, -0.03], P = .01), reviewed the source literature of heterogeneity, and found nothing. And the meta-analysis results did not change significantly due to heterogeneity, so we considered that the source of heterogeneity was caused by differences in treatment courses and medication.

3.6. The effect of probiotics on blood lipid levels

A total of 12 studies reported changes in total cholesterol (TC) levels from baseline (Fig. 8A): the analysis showed that TC levels were significantly reduced after probiotic intervention, (MD = -6.21, 95% CI [-14.59, 2.16], P = .15). A total of 15 studies

reported changes in triglyceride (TG) compared to pre-baseline (Fig. 8B): the analysis showed that TG levels were significantly reduced after probiotic intervention, (MD = -17.30, 95%CI [-30.27, -4.33], P = .009). A total of 11 studies reported changes in HDL-C from baseline (Fig. 8C): the analysis showed that HDL-C levels were elevated after probiotic intervention, (MD = 3.37, 95% CI [0.48, 6.27], P = .02). A total of 11 studies reported changes in LDL-C from baseline (Fig. 8D): the analysis showed that after probiotic intervention, LDL-C was elevated, (MD = 0.89, 95% CI [-3.46, 5.24], P = .15).

Due to the significant differences in the results of blood lipid levels, (TC, $I^2 = 88$, TG, $I^2 = 92$, HDL-C, $I^2 = 58$, LDL-C, $I^2 = 68\%$). In the TC study, we found that after excluding Famouri, Kobyliak, Manzhalii, Shavakhi and other studies, the heterogeneity was significantly reduced, $I^2 = 43\%$, P = .09, the analysis results showed: (MD = -4.90, 95% CI [-11.46, 1.67], P = .01). In the study of TG changes, after Kobyliak, Shavakhi and other

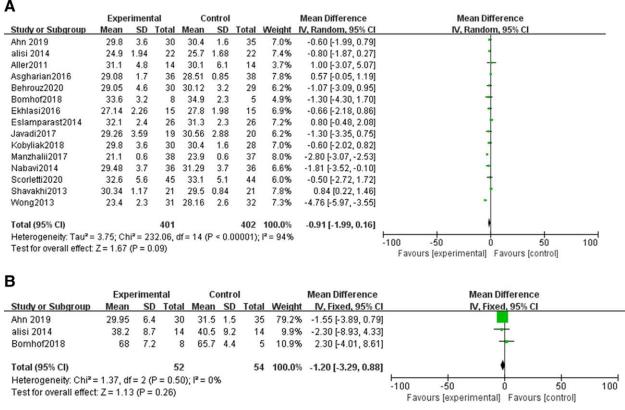


Figure 6. The total fat mass levels and BMI. A total of 3 studies reported changes from baseline in total fat mass levels (A): the results of the analysis showed that after probiotic intervention, total fat content was reduced; A total of 15 studies reported changes in BMI from baseline (B): the analysis showed that BMI was significantly reduced after probiotic intervention. BMI = body mass index.

studies, the heterogeneity was significantly reduced, $I^2 = 43\%$, P = .09, the analysis results showed: (MD = -2.49, 95% CI [-11.19, 6.21], P = .01); In the study of HDL-C changes, after excluding the study of Famouri, the heterogeneity was significantly reduced, $I^2 = 43\%$, P = .09, the analysis results showed: (MD = 2.14, 95% CI [-0.35, 4.62], P = .09); in the study of LDL-C changes, after excluding Wong's study, the heterogeneity results were better, $I^2 = 42\%$, P = .02, the analysis results showed: (MD = -0.73, 95% CI [-4.05, 2.59], P = .67).

3.7. The effect of probiotics on inflammatory factors

A total of 7 studies reported changes in IL-6 from baseline (Fig. 9A): the analysis showed that IL-6 was elevated after probiotic intervention, (MD = 1.41, 95% CI [0.21, 2.61], P = .02). A total of 8 studies reported changes in TNF- α from baseline (Fig. 9B): the analysis showed that after probiotic intervention, TNF- α decreased, (MD = -0.24, 95% CI [-1.25, 0.78], P = .64). A total of 4 studies reported changes in LPS from baseline (Fig. 9C): the analysis showed that LPS was reduced after probiotic intervention, (MD = -0.15, 95% CI [-0.42, 0.11], P = .26). A total of 4 studies reported changes in CRP compared to baseline (Fig. 9D): The analysis showed that after probiotic intervention, C-reactive protein (h-CRP) was elevated, (MD = -0.23, 95% CI [-1.46, 1.01], P = .72).

Due to the significant heterogeneity of the results (IL-6, I^2 = 88 TNF- α I^2 = 64 LPS I^2 = 94 h-CRP I^2 = 81%), we found that after excluding one by one comparison, in the IL-6 study, Ahn, Aller, Duseja, Bomhof and other studies have good homogeneity, I^2 = 27%, P = .25. The analysis results show: (MD = -0.10, 95% CI [-0.85, 0.66], P = .80), review Heterogeneity source literature, found that the heterogeneity was caused by Kobyliak's research, considering regional factors; in the TNF- α

study, after excluding Duseja, the heterogeneity results are now reduced, $I^2 = 22\%$, P = .26, The analysis results showed that (MD = -0.13, 95% CI [-0.69, 0.43], P = .66); in the LPS study, no source of heterogeneity was found. In the h-CRP study, after excluding Eslamparast and other studies, the heterogeneity results were significantly reduced, $I^2 = 0\%$, P = .26, the analysis results showed: (MD = 0.42, 95% CI [0.33, 0.51], P < .00001).

3.8. Effects of probiotics on ALT levels in children

A total of 3 studies reported the efficacy of probiotics in the treatment of children with NAFLD, but only ALT levels met the criteria for meta-analysis (Fig. 10). The analysis results showed that after probiotic intervention, the ALT level in the children group was significantly improved (MD = -15.27, 95% CI [-17.25, -13.29], P < .00001). After excluding Famouri's study, the heterogeneity was significantly reduced, $I^2 = 0\%$, P = .72, and the analysis results showed that (MD = -17.03, 95% CI [-19.16, -14.91], P < .00001). After reviewing the characteristics of the literature, it was found that the remaining two studies were conducted in Italy, so we considered that the heterogeneity was caused by regional factors.

3.9. Adverse reactions

A total of 7 studies explicitly reported adverse reactions (Fig. 11): the analysis showed that the incidence of adverse reactions was higher in the probiotic therapy group than in the placebo group (MD = 1.61, 95% CI [0.82, 3.15], P = .17). In addition, another study reported a higher frequency of flatulence in the metformin plus probiotic group, but no clear number of adverse reactions occurred. However, no major adverse reactions occurred.

	Expe	rimen	tal	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Ahn 2019	5.52	0.3	30	5.56	0.33	35	17.1%	-0.04 [-0.19, 0.11]	•
Aller2011	6.37	1.56	14	5.98	1.64	14	2.7%	0.39 [-0.80, 1.58]	†
Behrouz2020	4.81	0.46	30	5	0.47	29	15.1%	-0.19 [-0.43, 0.05]	•
Bomhof2018	5.61	0.59	8	7.28	0.64	5	6.2%	-1.67 [-2.36, -0.98]	
Ekhlasi2016	5.82	0.43	15	6.38	0.77	15	10.2%	-0.56 [-1.01, -0.11]	
Eslamparast2014	5.53	1.34	26	5.49	1.19	26	6.2%	0.04 [-0.65, 0.73]	1
Manzhalii2017	4.87	0.61	38	5.09	0.67	37	13.8%	-0.22 [-0.51, 0.07]	•
Nabavi2014	4.96	0.53	36	5	0.68	36	14.0%	-0.04 [-0.32, 0.24]	•
Scorletti2020	5.9	2.3	45	5.9	2.1	44	4.1%	0.00 [-0.91, 0.91]	1
Shavakhi2013	4.43	1.07	31	4.85	1.57	32	6.6%	-0.42 [-1.08, 0.24]	
Wong2013	5.3	1.5	10	6	0.3	10	3.9%	-0.70 [-1.65, 0.25]	1
Total (95% CI)			283			283	100.0%	-0.27 [-0.48, -0.06]	
Heterogeneity: Tau ² =	= 0.06; C	hi ^z = 2	7.65, df	f = 10 (P	= 0.00)2); l ^z =	64%		
Test for overall effect	Z = 2.55	i (P = 0).01)			2.2			-100 -50 0 50 10 Favours [experimental] Favours [control]

В

	Exp	eriment	tal	С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI
Ahn 2019	14.1	10.62	30	12.1	8.9	35	0.8%	2.00 [-2.81, 6.81]	+
Aller2011	14.3	6.9	14	14.6	6.4	14	0.7%	-0.30 [-5.23, 4.63]	+
Bomhof2018	51.8	9.6	8	46.9	10.5	5	0.1%	4.90 [-6.46, 16.26]	<u>+</u>
Ekhlasi2016	1.8	0.61	15	2.56	0.59	15	96.6%	-0.76 [-1.19, -0.33]	
Scorletti2020	13.1	7.5	45	13.6	7.6	44	1.8%	-0.50 [-3.64, 2.64]	+
Total (95% CI)			112			113	100.0%	-0.72 [-1.14, -0.30]	
Heterogeneity: Chi ² =	2.25, df	= 4 (P =	0.69);	I ² = 0%					
Test for overall effect	Z = 3.36	6 (P = 0.	0008)						-100 -50 0 50 100 Favours [experimental] Favours [control]

С

Exp	eriment	tal	C	ontrol			Mean Difference		N	lean Differen	ce	
Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl		IV,	Random, 95%	6 CI	
68.6	46.11	30	59.4	35.4	35	0.0%	9.20 [-11.04, 29.44]				—	
3.3	0.3	22	3.5	0.6	22	31.9%	-0.20 [-0.48, 0.08]					
4.2	2.4	14	4.3	3.4	14	1.3%	-0.10 [-2.28, 2.08]			+		
5.51	1.02	8	5.27	1.03	5	4.4%	0.24 [-0.91, 1.39]			t		
2.2	1.5	19	3	1.4	16	6.1%	-0.80 [-1.76, 0.16]			-		
0.75	0.46	15	0.67	0.28	15	32.6%	0.08 [-0.19, 0.35]			•		
2.02	0.6	26	2.51	0.8	26	23.7%	-0.49 [-0.87, -0.11]			1		
		134			133	100.0%	-0.19 [-0.44, 0.06]					
0.03; C	hi² = 8.8	8. df =	6 (P = 0).18); P	= 32%	0			1	<u> </u>	+	100
										0		100
	Mean 68.6 3.3 4.2 5.51 2.2 0.75 2.02 0.03; C	Mean SD 68.6 46.11 3.3 0.3 4.2 2.4 5.51 1.02 2.2 1.5 0.75 0.46 2.02 0.6 0.03; Chi ² = 8.8	68.6 46.11 30 3.3 0.3 22 4.2 2.4 14 5.51 1.02 8 2.2 1.5 19 0.75 0.46 15 2.02 0.6 26	Mean SD Total Mean 68.6 46.11 30 59.4 3.3 0.3 22 3.5 4.2 2.4 14 4.3 5.51 1.02 8 5.27 2.2 1.5 19 3 0.75 0.46 15 0.67 2.02 0.6 26 2.51 134 colspan="3">134	Mean SD Total Mean SD 68.6 46.11 30 59.4 35.4 3.3 0.3 22 3.5 0.6 4.2 2.4 14 4.3 3.4 5.51 1.02 8 5.27 1.03 2.2 1.5 19 3 1.4 0.75 0.46 15 0.67 0.28 2.02 0.6 26 2.51 0.8 134 134 134 134	Mean SD Total Mean SD Total 68.6 46.11 30 59.4 35.4 35 3.3 0.3 22 3.5 0.6 22 4.2 2.4 14 4.3 3.4 14 5.51 1.02 8 5.27 1.03 5 2.2 1.5 19 3 1.4 16 0.75 0.46 15 0.67 0.28 15 2.02 0.6 26 2.51 0.8 26 Total 133 Total Total	Mean SD Total Mean SD Total Weight 68.6 46.11 30 59.4 35.4 35 0.0% 3.3 0.3 22 3.5 0.6 22 31.9% 4.2 2.4 14 4.3 3.4 14 1.3% 5.51 1.02 8 5.27 1.03 5 4.4% 2.2 1.5 19 3 1.4 16 6.1% 0.75 0.46 15 0.67 0.28 15 32.6% 2.02 0.6 26 2.51 0.8 26 23.7% 134 133 100.0% 133 100.0% 100.3% 100.3%	Mean SD Total Mean SD Total Weight IV. Random, 95% C1 68.6 46.11 30 59.4 35.4 35 0.0% 9.20 [-11.04, 29.44] 3.3 0.3 22 3.5 0.6 22 31.9% -0.20 [-0.48, 0.08] 4.2 2.4 14 4.3 3.4 14 1.3% -0.10 [-2.28, 2.08] 5.51 1.02 8 5.27 1.03 5 4.4% 0.24 [-0.91, 1.39] 2.2 1.5 19 3 1.4 16 6.1% -0.80 [-1.76, 0.16] 0.75 0.46 15 0.67 0.28 15 32.6% 0.08 [-0.19, 0.35] 2.02 0.6 26 2.51 0.8 26 23.7% -0.49 [-0.87, -0.11] Total Total Total 5 4.4% 0.06 [-0.44, 0.06] 0.03; Chi ² = 8.88, df = 6 (P = 0.18); P = 32% 100.0% -0.19 [-0.44, 0.06] 10.3% <td>$\begin{array}{c c c c c c c c c c c c c c c c c c c$</td> <td>$\begin{array}{c c c c c c c c c c c c c c c c c c c$</td> <td>$\begin{array}{c c c c c c c c c c c c c c c c c c c$</td> <td>Mean SD Total Mean SD Total Weight W. Random, 95% Cl V. Random, 95% Cl 68.6 46.11 30 59.4 35.4 35 0.0% 9.20 [-11.04, 29.44] 1.33 0.3 22 3.5 0.6 22 31.9% -0.20 [-0.48, 0.08] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] <</td>	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Mean SD Total Mean SD Total Weight W. Random, 95% Cl V. Random, 95% Cl 68.6 46.11 30 59.4 35.4 35 0.0% 9.20 [-11.04, 29.44] 1.33 0.3 22 3.5 0.6 22 31.9% -0.20 [-0.48, 0.08] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] -0.20 [-0.48, 0.06] <

Figure 7. The blood glucose and insulin levels. A total of 11 studies reported changes in blood glucose from baseline (A): the analysis showed that blood glucose levels decreased after probiotic intervention. A total of 5 studies reported changes in insulin from baseline (B): the analysis showed that after probiotic intervention, insulin levels decreased. A total of 7 studies reported changes from baseline in insulin resistance (C): the analysis showed that insulin resistance was reduced after probiotic intervention.

3.10. The effect of different treatment cycles on the outcome of NAFLD

Due to the different durations of each study, in order to determine the correlation between the improvement effect of probiotic preparations and the duration of treatment, we conducted a subgroup analysis through studies with a duration of greater than or equal to 12 weeks and studies with a duration of less than 12 weeks, the course of treatment is greater than or equal to 12 weeks as a group. The results of the analysis showed that after excluding studies with heterogeneity sources, the improvement of ALT, GGT, TG, blood glucose and other outcomes in studies with a course of treatment greater than or equal to 12 weeks was significantly better than that of studies with a treatment course of less than 12 weeks; while AST, TC, and BMI were on the contrary. In addition, HDL-C increased in both studies, and the increase in studies with duration of treatment greater than or equal to 12 weeks was lower than that in studies with duration of treatment less than 12 weeks. In a subgroup analysis, we found that probiotic therapy had a statistically significant improvement in BMI when the course of treatment was less than 12 weeks. The specific data are shown in Figures 12 and 13.

4. Discussion

Obesity, type 2 diabetes, and lipid metabolism disorders are closely related to nonalcoholic fatty liver disease.^[42] All of these diseases can lead to the accumulation of fat in the liver, the accumulation of free fatty acids in the liver, resulting in hepatotoxicity, and promoting the progression of nonalcoholic fatty liver disease to nonalcoholic fatty liver disease, steatohepatitis, liver fibrosis, and liver cirrhosis.^[43] In addition, high insulin levels also increase TG content and accelerate liver fat accumulation.^[44]

The gut microbiota is closely related to human health, and the microbes and their metabolites in the gut play an important

		mental			ontrol	T . 4 . 1			Difference	Mean Difference
tudy or Subgroup	Mean		<u>fotal</u>	Mean	SD		Weight		ndom, 95% Cl	IV, Random, 95% Cl
hn 2019	179.8	12.3	30	184.3	36.8	35	6.6%		[-17.46, 8.46]	
ller2011	200.9	33.1	14	204.7	54	14	1.6%		-36.98, 29.38]	
hong2021	79.56		19	81	19.08	16	6.1%		-15.33, 12.45]	
amouri2016		47.87		105.43	23.56	32	4.2%		[21.14, 58.12]	
obyliak2018	106.2	5.58		106.43	6.84	28	13.9%		3 [-3.46, 3.00]	T
obyliak 2018	101.16	3.96		107.43	4.14	22	14.4%		7 [-8.57, -3.97]	
obyliak2019	105.48	5.4		108.43	4.68	24	14.1%		5 [-5.75, -0.15]	_1
anzhalii2017	97.2	3.6	38	108	3.6	37	14.7%		[-12.43, -9.17]	•
abavi2014	172.61	42.6		202.88	33.53	36	4.5%		47.98, -12.56]	
corletti2020	89.28	21.6	45	84.6	19.8	44	9.6%		[-3.93, 13.29]	
navakhi2013	183.3	25.2	31	205.5	39	32	5.1%		[-38.36, -6.04]	
jro2011	90	10.8	10	90	23.4	10	5.2%	0.00	-15.97, 15.97]	
otal (95% CI)			337				100.0%	-3.74	4 [-8.22, 0.74]	•
eterogeneity: Tau² = est for overall effect: .				11 (P <	0.00001); l² = 8	8%			-100 -50 0 50 10 Favours [experimental] Favours [control]
										ratoura (experimental) ratoura (control)
	Expe	rimenta	al	(Control			Mean (Difference	Mean Difference
Study or Subgroup	Mean	SD	 Total	Mean		Total	Weight		ndom, 95% Cl	IV, Random, 95% Cl
Ahn 2019	177.3	139	30	150.4			0.4%		29.08, 82.88]	
alisi 2014	102	10	22	110			12.0%		13.62, -2.38]	-
Aller2011	147.2	48.6	14	150.9		14	0.7%		44.60, 37.20]	
Behrouz2020		161.7	30	145.3			0.3%		22.62, 98.42]	
Chong2021	43.02	25.56	19	34.38		16	4.5%		[-5.85, 23.13]	+
Ekhlasi2016	186.87	26.94	15				3.5%		[1.85, 35.95]	
Famouri2016		19.14	32			32	3.5%		[-25.57, 8.19]	
Kobyliak2018	43.92	15.66	30	35.82			12.0%		[2.42, 13.78]	
Kobyliak 2018	43.92	0.9	26	35.48			16.7%		6 [7.06, 9.86]	
Kobyliak2019	43.92	1.08	26	39.24			17.0%		8 [3.79, 5.57]	
Manzhalii2017	23.04	0.19	38	23.76			16.8%		2 [-1.94, 0.50]	
Nabavi2014	206.02		36				1.0%			
Scorletti2020			45						[-1.16, 67.38]] [-5.32, 8.92]	<u> </u>
	30.6 188.7	10.8 68.9	31	28.8 149.7			10.2% 1.2%			
Shavakhi2013			31			32	1.2%	39.00	[7.72, 70.28]	•
Shavakhi2013 Total (95% CI)	188.7	68.9	31 394	149.7	57	32 386	1.2% 100.0%	39.00	[7.72, 70.28] 4 [0.47, 7.60]	• • • • • •
Shavakhi2013	188.7 = 19.27; C	68.9 hi ^z = 133	31 394 3.75, d	149.7	57	32 386	1.2% 100.0%	39.00	[7.72, 70.28] 4 [0.47, 7.60]	100 -50 0 50 100 Favours lexperimental Favours (control)
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ²	188.7 = 19.27; C	68.9 hi ^z = 133	31 394 3.75, d	149.7	57	32 386	1.2% 100.0%	39.00	[7.72, 70.28] 4 [0.47, 7.60]	-100 -50 0 50 100 Favours [experimental] Favours [control]
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ²	188.7 *= 19.27; C :t: Z = 2.22	68.9 hi ^z = 133	31 394 3.75, d 3)	149.7 f= 13 (P	57	32 386	1.2% 100.0%	39.00 4.04	[7.72, 70.28] 4 [0.47, 7.60]	
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ²	188.7 *= 19.27; C :t: Z = 2.22 Expe	68.9 hi ² = 13: (P = 0.0: erimenta	31 394 3.75, d 3) al	149.7 f= 13 (P	57 < 0.000	32 386 101); I ² =	1.2% 100.0%	39.00 4.04 Mean	(7.72, 70.28) 4 [0.47, 7.60]	Favours (experimental) Favours (control)
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup	188.7 = 19.27; C t: Z = 2.22 Exp Mean	68.9 hi ^z = 13: (P = 0.0: erimenta SD	31 394 3.75, d 3) al <u>Total</u>	149.7 f = 13 (P C <u>Mean</u>	 57 < 0.000 Control SD 	32 386 101); I² = <u>Total</u>	1.2% 100.0% 90% Weight	39.00 4.0 Mean I IV, Ra	(7.72, 70.28) 4 [0.47, 7.60] Difference Indom, 95% CI	Favours [experimental] Favours [control] Mean Difference
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ^a Test for overall effec Study or Subgroup Aller2011	188.7 = 19.27; C t: Z = 2.22 Exp Mean 43	68.9 hi ^z = 133 (P = 0.03 erimenta <u>SD</u> 11.6	31 394 3.75, d 3) al <u>Total</u> 14	149.7 f= 13 (P <u>C Mean</u> 43.3	57 < 0.000 Control SD 8.9	32 386 101); I ² = <u>Total</u> 14	1.2% 100.0% 90% <u>Weight</u> 8.7%	39.00 4.0 Mean I <u>IV, Ra</u> -0.3	(7.72, 70.28) 4 [0.47, 7.60] Difference indom, <u>95% CI</u> 30 [-7.96, 7.36]	Favours [experimental] Favours [control] Mean Difference
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020	188.7 = 19.27; C t: Z = 2.22 <u>Exp</u> <u>Mean</u> 43 39	68.9 $hi^{2} = 133$ (P = 0.03) eriments <u>SD</u> 11.6 6	31 394 3.75, d 3) al <u>Total</u> 14 30	149.7 f= 13 (P <u>C</u> <u>Mean</u> 43.3 40	 57 < 0.000 control SD 8.9 7 	32 386 101); I ² = <u>Total</u> 14 29	1.2% 100.0% 90% Weight 8.7% 9.2%	39.00 4.0 Mean <u>IV. Ra</u> -0.3 -1.0	(7.72, 70.28) 4 [0.47, 7.60] Difference <u>indom, 95% CI</u> 30 [-7.96, 7.36] 10 [-4.33, 2.33]	Favours (experimental) Favours (control) Mean Difference
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ^a Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021	188.7 = 19.27; C :t: Z = 2.22 <u>Exp</u> <u>Mean</u> 43 39 21.6	68.9 hi ² = 133 (P = 0.03 erimenta <u>SD</u> 11.6 6 1.8	31 394 3.75, d 3) al <u>Total</u> 14 30 19	149.7 f= 13 (P 0 <u>Mean</u> 43.3 40 19.08	 57 < 0.000 Control SD 8.9 7 6.3 	32 386 101); I ² = <u>Total</u> 14 29 16	1.2% 100.0% 90% <u>Weight</u> 8.7% 9.2% 9.3%	39.00 4.04 Mean 1 <u>IV, Ra</u> -0.3 -1.0 2.5	(7.72, 70.28) 4 [0.47, 7.60] Difference <u>indom, 95% CI</u> 30 [-7.96, 7.36] 0 [-4.33, 2.33] 52 [-0.67, 5.71]	Favours (experimental) Favours (control) Mean Difference
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016	188.7 = 19.27; C :t: Z = 2.22 <u>Exp</u> <u>Mean</u> 43 39 21.6 49.19	68.9 hi ² = 133 (P = 0.03 erimenta <u>SD</u> 11.6 6 1.8 12.2	31 394 3.75, d 3) al <u>Total</u> 14 30 19 15	149.7 f= 13 (P 0 <u>Mean</u> 43.3 40 19.08 38.52	control 50 8.9 7 6.3 8.17	32 386 101); I ² = <u>Total</u> 14 29 16 15	1.2% 100.0% 90% Weight 8.7% 9.2% 9.3% 8.7%	39.00 4.04 Mean I <u>IV, Ra</u> -0.3 -1.0 2.5 10.6	(7.72, 70.28) 4 (0.47, 7.60) Difference <u>indom, 95% CI</u> 30 (-7.96, 7.36) 30 (-4.33, 2.33) 22 (-0.67, 5.71) 7 (3.24, 18.10)	Favours (experimental) Favours (control) Mean Difference
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Exhlasi2016 Farnouri2016	188.7 = 19.27; C :t: Z = 2.22 <u>Mean</u> 43 39 21.6 49.19 46.75	68.9 hi ^z = 133 (P = 0.03 erimenta <u>SD</u> 11.6 6 1.8 12.2 11.32	31 394 3.75, d 3) al <u>Total</u> 14 30 19 15 32	149.7 f= 13 (P 0 <u>Mean</u> 43.3 40 19.08 38.52 36.53	57 57 50 50 50 50 50 50 50 50 50 50	32 386 101); I ² = <u>Total</u> 14 29 16 15 32	1.2% 100.0% 90% Weight 8.7% 9.2% 9.3% 8.7% 9.0%	39.00 4.0 Mean 1 <u>IV. Ra</u> -0.3 -1.0 2.5 10.6 10.2	(7.72, 70.28) 4 (0.47, 7.60) Difference indom, 95% CI 30 [-7.96, 7.36] 00 [-4.33, 2.33] 32 [-0.67, 5.71] 7 [3.24, 18.10] 2 [4.94, 15.50]	Favours (experimental) Favours (control) Mean Difference
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Famouri2016 Kobyliak2018	188.7 = 19.27; C tt Z = 2.22 <u>Mean</u> 43 39 21.6 49.19 46.75 25.38	68.9 hi ^z = 133 (P = 0.03 erimenta 5D 11.6 6 1.8 12.2 11.32 9	31 394 3.75, d 3) al <u>Total</u> 14 30 19 15 32 30	149.7 f= 13 (P 0 <u>Mean</u> 43.3 40 19.08 38.52 36.53 25.38	control 30.000 30.000 30.000 8.9 7 6.3 8.9 7 6.3 8.17 10.21 8.28	32 386 101); I ² = <u>Total</u> 14 29 16 15 32 28	1.2% 100.0% 90% Weight 8.7% 9.3% 8.7% 9.0% 9.1%	39.00 4.0 Mean 1 <u>IV, Ra</u> -0.3 -1.0 2.5 10.6 10.2 0.0	(7.72, 70.28) 4 (0.47, 7.60) Difference indom, 95% CI 30 [-7.96, 7.36] 00 [-4.33, 2.33] 52 [-0.67, 5.71] 7 (3.24, 18.10) 10 [-4.45, 4.45]	Favours (experimental) Favours (control) Mean Difference
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ^a Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Exhlasi2016 Famouri2016 Kobyliak2018	188.7 = 19.27; C = 2.22 Exp Mean 43 39 21.6 49.19 46.75 25.38 26.28	68.9 hi ^z = 13: (P = 0.0: arimenta 5D 11.6 1.8 12.2 11.32 9 10.44	31 394 3.75, d 3) al <u>Total</u> 14 30 19 15 32 30 26	149.7 f= 13 (P 0 <u>Mean</u> 43.3 40 19.08 38.52 36.53 25.38 25.38	control 30 30 30 30 30 30 30 30 30 30 30 30 30	32 386 101); I ² = Total 14 29 16 15 32 28 22	1.2% 100.0% 90% Weight 8.7% 9.2% 9.3% 8.7% 9.0% 9.0%	39.00 4.0 Mean 1 <u>IV. Ra</u> -0.3 -1.0 2.5 10.6 10.2 0.0 0.9	(7.72, 70.28) 4 [0.47, 7.60] Difference indom, 95% CI 30 [-7.96, 7.36] 10 [-4.32, 2.33] 2 [-0.67, 5.71] 7 [3.24, 18.10] 2 [4.94, 15.50] 0 [-4.45, 4.45] 0 [-4.45, 4.45]	Favours [experimental] Favours [control] Mean Difference
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Exhlasi2016 Kobyliak2018 Kobyliak2019	188.7 = 19.27; C tt Z = 2.22 <u>Mean</u> 43 39 21.6 49.19 46.75 25.38 26.28 30.6	68.9 hi ² = 13: (P = 0.0: erimenta 5D 11.6 6 1.8 12.2 11.32 11.32 10.44 9.18	31 394 3.75, d 3) al <u>Total</u> 14 30 19 15 32 30 26 26	149.7 f= 13 (P 0 <u>Mean</u> 43.3 40 19.08 38.52 36.53 25.38 25.38 25.2	57 57 50 50 50 50 50 50 50 50 50 50	32 386 101); I ² = Total 14 29 16 15 32 28 22 24	1.2% 100.0% 90% Weight 8.7% 9.2% 9.3% 8.7% 9.0% 9.0% 9.1%	39.00 4.04 Mean 1 10, Ra -0.3 -1.0 2.5 10.6 10.2 0.0 0.9 5.4	(7.72, 70.28) 4 (0.47, 7.60) Difference <u>indom, 95% CI</u> 30 (-7.96, 7.36) 7 (3.24, 2.33) 52 (-0.67, 5.71) 7 (3.24, 18.10) 10 (-4.45, 4.45) 30 (-4.65, 6.45) 30 (-4.65, 6.45) 30 (-4.65, 6.45)	Favours [experimental] Favours [control] Mean Difference
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Farnouri2016 Kobyliak2018 Kobyliak2018 Nabavl2014	188.7 = 19.27; C t: Z = 2.22 Mean 43 39 21.6 46.75 25.38 26.28 30.6 23.94	68.9 hi ² = 13: (P = 0.03 erimenta 5D 11.6 6 1.8 12.2 11.3 9 10.44 9.18 4.14	31 394 3.75, d 33) al <u>Total</u> 14 30 19 15 32 30 26 26 36	149.7 f= 13 (P 0 <u>Mean</u> 43.3 40 19.08 38.52 36.53 25.38 25.38 25.38 25.2 50.84	57 57 50 50 50 50 50 50 50 50 50 50	32 386 101); I ² = Total 14 29 16 15 32 28 22 24 36	1.2% 100.0% 90% Weight 8.7% 9.2% 9.3% 8.7% 9.0% 9.1% 9.1% 9.1% 9.2%	39.00 4.04 Mean I IV, Ra -0.3 -1.0 2.5 10.6 10.2 0.0 0.9 5.4 -26.90 [-	(7.72, 70.28) 4 [0.47, 7.60] 0 [4.33, 2.33] 0 [-7.96, 7.36] 0 [-4.33, 2.33] 2 [-0.67, 5.71] 7 [3.24, 18.10] 2 [4.94, 15.50] 0 [-4.45, 4.45] 00 [-4.45, 4.45] 3 0 [0.46, 10.34] 3 0.39, -23.41]	Favours (experimental) Favours (control) Mean Difference
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Stucky or Subgroup. Aller2011 Behrouz2020 Chong2021 Exhlasi2016 Famouri2016 Famouri2016 Kobyliak2019 Nabavi2014 Scorletti2020	188.7 = 19.27; C Expo Mean 43 39 21.6 49.19 46.75 25.38 26.28 30.6 23.94 40	68.9 hi ^z = 13: (P = 0.03 erimenta 5D 11.6 6 1.8 12.2 11.32 9 10.44 9.18 4.14 4.5	31 394 3.75, d 33) al Total 14 30 19 15 32 30 26 26 36 36 45	149.7 f= 13 (P C Mean 43.3 40 19.08 38.52 36.53 25.38 25.38 25.38 25.2 50.84 21.6	control so 8.9 7 6.3 8.17 10.21 8.28 9.18 8.64 9.84 5.4	32 386 101); I [≠] = Total 14 29 16 15 32 28 22 24 36 44	1.2% 100.0% 90% 8.7% 9.2% 9.3% 8.7% 9.0% 9.1% 9.0% 9.1% 9.0% 9.1% 9.2% 9.3%	39.00 4.04 Mean i 10, Ra -0.3 -1.0 2.5 10,6 10,2 0.0 0.9 5.4 -26,90 [18,40	[7.72, 70.28] 4 [0.47, 7.60] Difference indom, 95% CI 00 [-7.96, 7.36] 00 [-4.33, 2.33] 52 [-0.67, 5.71] 7 [3.24, 18.10] 2 [4.94, 15.50] 10 [-4.65, 6.45] 0 [-4.6, 10.34] :30.39, -23.41] :16.33, 20.47]	Favours (experimental) Favours (control) Mean Difference
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Exhlasi2016 Famouri2016 Famouri2016 Kobyliak 2018 Kobyliak 2018 Kobyliak2019 Nabavi2014 Scorletti2020	188.7 = 19.27; C t: Z = 2.22 Mean 43 39 21.6 46.75 25.38 26.28 30.6 23.94	68.9 hi ² = 13: (P = 0.03 erimenta 5D 11.6 6 1.8 12.2 11.3 9 10.44 9.18 4.14	31 394 3.75, d 33) al <u>Total</u> 14 30 19 15 32 30 26 26 36	149.7 f= 13 (P 0 <u>Mean</u> 43.3 40 19.08 38.52 36.53 25.38 25.38 25.38 25.2 50.84	57 57 50 50 50 50 50 50 50 50 50 50	32 386 101); I ² = Total 14 29 16 15 32 28 22 24 36	1.2% 100.0% 90% Weight 8.7% 9.2% 9.3% 8.7% 9.0% 9.1% 9.1% 9.1% 9.2%	39.00 4.04 Mean i 10, Ra -0.3 -1.0 2.5 10,6 10,2 0.0 0.9 5.4 -26,90 [18,40	(7.72, 70.28) 4 [0.47, 7.60] 0 [4.33, 2.33] 0 [-7.96, 7.36] 0 [-4.33, 2.33] 2 [-0.67, 5.71] 7 [3.24, 18.10] 2 [4.94, 15.50] 0 [-4.45, 4.45] 00 [-4.45, 4.45] 3 0 [0.46, 10.34] 3 0.39, -23.41]	Favours [experimental] Favours [control] Mean Difference
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Famouri2016 Famouri2016 Kobyliak2018 Kobyliak2018 Kobyliak2018 Kobyliak2018 Scorletti2020 Wong2013 Total (95% CI)	188.7 = 19.27; C = 2.22 Expo Mean 43 39 21.6 49.19 46.75 25.38 26.28 30.6 23.94 40 23.4	68.9 hi ^z = 133 (P = 0.03 11.6 6 1.8 12.2 11.32 9 10.44 9.18 4.14 4.5 5.4	31 394 3.75, d 3) al Total 14 30 19 15 32 30 26 26 36 45 10 283	149.7 f= 13 (P 0 <u>Mean</u> 43.3 40 19.08 38.52 36.53 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.2 25.2 25.2 25.2 25.2 25.2 25.2 25.	57 57 57 50 50 50 50 50 50 50 50 50 50	32 386 10 (0); F [≠] = Total 14 29 16 15 32 28 22 24 36 44 10 270	1.2% 100.0% 90% 90% 9.0% 9.2% 9.3% 9.0% 9.1% 9.0% 9.1% 9.2% 9.2% 9.2% 100.0%	39.00 4.0- 4.0- 4.0- 7.0.3 -1.0. 2.6 10.2 2.6 10.2 0.0 0.0 0.0 0.0 0.0 5.4 -26.90 [18.40 1.6 18.40 1.6 1.93	[7.72, 70.28] 4 [0.47, 7.60] Difference indom, 95% CI 00 [-7.96, 7.36] 00 [-4.33, 2.33] 52 [-0.67, 5.71] 7 [3.24, 18.10] 2 [4.94, 15.50] 10 [-4.65, 6.45] 0 [-4.6, 10.34] :30.39, -23.41] :16.33, 20.47]	Favours [experimental] Favours [control] Mean Difference
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Famouri2016 Kobyliak2018 Kobyliak2018 Kobyliak2018 Nabavi2014 Scorletti2020 Wong2013 Total (95% CI) Heterogeneity: Tau ²	188.7 = 19.27; C t: Z = 2.22 Mean 43 39 21.6 49.19 46.75 25.38 26.28 30.6 23.94 40 23.4 = 198.36;	68.9 $hi^{\mu} = 13.3$ $(P = 0.03)^{\mu}$ 11.6 6 11.6 12.2 11.32 9 10.44 4.14 4.14 4.5 5.4 $Chi^{2} = 5$	31 394 3.75, d 3.75, d 3.75, d 14 30 19 15 32 30 26 36 36 36 45 10 283 513.42	149.7 f= 13 (P 0 <u>Mean</u> 43.3 40 19.08 38.52 36.53 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.2 25.2 25.2 25.2 25.2 25.2 25.2 25.	57 57 57 50 50 50 50 50 50 50 50 50 50	32 386 10 (0); F [≠] = Total 14 29 16 15 32 28 22 24 36 44 10 270	1.2% 100.0% 90% 90% 9.0% 9.2% 9.3% 9.0% 9.1% 9.0% 9.1% 9.2% 9.2% 9.2% 100.0%	39.00 4.0- 4.0- 4.0- 7.0.3 -1.0. 2.6 10.2 2.6 10.2 0.0 0.0 0.0 0.0 0.0 5.4 -26.90 [18.40 1.6 18.40 1.6 1.93	[7.72, 70.28] 4 [0.47, 7.60] Difference indom, 95% CI 00 [-7.96, 7.36] 00 [-4.33, 2.33] 52 [-0.67, 7.57] 7 [3.24, 18.10] 2 [4.94, 15.50] 10 [-4.65, 6.45] 10 [-4.65, 6.45] 30.39, -23.41] [16.33, 20.47] 32 [-1.91, 5.15]	Favours [experimental] Favours [control]
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Famouri2016 Kobyliak2018 Kobyliak2018 Kobyliak2018 Nabavi2014 Scorletti2020 Wong2013 Total (95% CI) Heterogeneity: Tau ²	188.7 = 19.27; C t: Z = 2.22 Mean 43 39 21.6 49.19 46.75 25.38 26.28 30.6 23.94 40 23.4 = 198.36;	68.9 $hi^{\mu} = 13.3$ $(P = 0.03)^{\mu}$ 11.6 6 11.6 12.2 11.32 9 10.44 4.14 4.14 4.5 5.4 $Chi^{2} = 5$	31 394 3.75, d 3.75, d 3.75, d 14 30 19 15 32 30 26 36 36 36 45 10 283 513.42	149.7 f= 13 (P 0 <u>Mean</u> 43.3 40 19.08 38.52 36.53 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.2 25.2 25.2 25.2 25.2 25.2 25.2 25.	57 57 57 50 50 50 50 50 50 50 50 50 50	32 386 10 (0); F [≠] = Total 14 29 16 15 32 28 22 24 36 44 10 270	1.2% 100.0% 90% 90% 9.0% 9.2% 9.3% 9.0% 9.1% 9.0% 9.1% 9.2% 9.2% 9.2% 100.0%	39.00 4.0- 4.0- 4.0- 7.0.3 -1.0. 2.6 10.2 0.0 0.0 0.0 0.0 5.4 -26.90 [18.40 1.6 18.40 1.6 1.93	[7.72, 70.28] 4 [0.47, 7.60] Difference indom, 95% CI 00 [-7.96, 7.36] 00 [-4.33, 2.33] 52 [-0.67, 7.57] 7 [3.24, 18.10] 2 [4.94, 15.50] 10 [-4.65, 6.45] 10 [-4.65, 6.45] 30.39, -23.41] [16.33, 20.47] 32 [-1.91, 5.15]	Favours (experimental) Favours (control)
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ^a Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Famouri2016 Kobyliak2018 Kobyliak2018 Kobyliak2018 Kobyliak2014 Scorletti2020 Wong2013	188.7 = 19.27; C = 19.27; C = Mean 39 21.6 49.19 46.75 25.38 26.28 30.6 23.94 40 23.4 = 198.36; ct: Z = 0.45	68.9 hi [#] = 13: (P = 0.0; 11.6 6 6 1.8 12.2 11.32 9.10.44 9.18 4.14 4.5.4 Chi ² = 5 (P = 0.6	31 394 3.75, d 33) al <u>Total</u> 14 30 19 15 32 30 26 36 36 36 36 36 3513.42 36)	149.7 f= 13 (P 0 <u>Mean</u> 43.3 40 19.08 38.52 36.53 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.2 25.2 25.2 25.2 25.2 25.2 25.2 25.	 57 50 50 50 8.9 7 6.8 8.9 7 7 10.21 8.28 8.64 9.18 8.64 9.18 8.64 9.18 8.64 1.8 (P < 0.0000000000000000000000000000000000	32 386 701 14 29 16 15 32 28 22 24 34 10 270 00001);	1.2% 100.0% 90% 90% 9.0% 9.2% 9.3% 9.0% 9.1% 9.0% 9.1% 9.2% 9.2% 9.2% 100.0%	39.00 4.0- 4.0- 4.0- 7.0.3 -1.0. 2.6 10.2 0.0 0.0 0.0 0.0 5.4 -26.90 [18.40 1.6 18.40 1.6 1.93	[7.72, 70.28] 4 [0.47, 7.60] Difference indom, 95% CI 00 [-7.96, 7.36] 00 [-4.33, 2.33] 52 [-0.67, 5.71] 10 [-4.45, 4.45] 00 [-4.45, 4.45] 00 [-4.65, 6.45] 00 [-4.65, 0.34] 16.33, 20.47] 12 [-1.91, 5.15] [-6.53, 10.38]	Favours [experimental] Favours [control]
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Exhlasi2016 Famouri2016 Famouri2016 Kobyliak2018 Kobyliak2018 Kobyliak2018 Kobyliak2018 Scorletti2020 Wong2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effect	188.7 = 19.27; C t Z = 2.22 Mean 40, 39 21.6 49.19 46.75 26.28 30.6 23.94 40 23.4 = 198.36; ct: Z = 0.45	68.9 hi ^p = 13: (P = 0.0: <u>SD</u> 11.6 6 1.8 12.2 11.32 9 10.44 4.5 5.4 Chi ² = 6 (P = 0.6 eriment	31 394 3.75, d 33) al <u>Total</u> 14 30 19 15 32 30 26 26 26 26 26 36 45 10 283 3513.42 26 513.42	149.7 f= 13 (P <u>Mean</u> 43.3 43.3 43.3 26.2 25.38 25.39 25.38 25.39	57 57 50 50 50 50 50 50 50 50 50 50	32 386 101); *= Total 14 29 16 15 32 28 22 24 36 44 10 270 00001); ntrol	1.2% 100.0% 90% 92% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.3% 9.2% 100.0% P = 98%	39.00 4.0 4.0 4.0 5.0 7 5.0 5.4 10.2 0.0 9 5.4 10.2 0.0 9 5.4 10.2 0.0 9 10.2 10.2 10.2 10.2 10.2 10.2 10.2 10.2	(7.72, 70.28) 4 [0.47, 7.60] Difference mdom, 95% CI 30 [-7.96, 7.36] 0 [-4.33, 2.33] 52 [-0.67, 5.71] 0 [-4.45, 4.45] 0 [-4.65, 6.45] 0 [-4.65, 6.45] 0 [-4.65, 6.45] 0 [-4.65, 6.45] 0 [-4.65, 6.45] 1 (-6.33, 20.47] 52 [-1.91, 5.15] 1 (-6.53, 10.38] Mean Different	Favours [experimental] Favours [control]
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Famouri2016 Kobyliak2018 Kobyliak2018 Kobyliak2018 Scorletti2020 Wong2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effect Study or Subgroup	188.7 = 19.27; C Exp Mean 43 39 21.6 49.19 46.75 25.38 26.28 30.6 23.94 40 23.4 = 198.36; ct: Z = 0.45 Exq Mean	68.9 hi ^a = 13: (P = 0.0: SD 11.6 6 1.8 12.2 11.32 9.10.44 9.18 4.14 5.4 Chi ² = 5 (P = 0.6 Chi ² = 6 Chi ² = 7 Chi ² = 6 Chi ² = 7 Chi ² = 7 Ch	31 394 3.75, d 3.75, d 1.33) al <u>Total</u> 14 30 19 15 32 30 10 26 36 45 50 10 283 35 13.422 369 45 10 283 35 50 10 10 10 10 10 10 10 10 10 1	149.7 f= 13 (P (C Mean 43.3 40 19.08 38.52 36.53 25.38 25.38 25.38 25.38 25.38 25.38 25.38 21.78 (f= 10) (f= 10	 57 < 0.000 SD 8.9 7 6.3 8.17 10.21 8.28 8.64 9.18 8.64 9.84 5.4 1.8 (P < 0.0 Co Mean 	32 386 101); *= Total 14 29 16 15 32 28 22 28 22 24 36 44 10 270 00001); mtrol SC	1.2% 100.0% 90% Weight 8.7% 9.2% 9.2% 9.3% 9.0% 9.1% 9.2% 9.3% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.1% 9.2	39.00 4.0 4.0 4.0 7.0 7.0 7.0 7.0 7.0 7.0 7.0 7.0 7.0 7	[7.72, 70.28] 4 [0.47, 7.60] Difference mdom, 95% CI 30 [-7.96, 7.36] 30 [-4.33, 2.33] 52 [-0.67, 5.71] 7 [3.24, 18.10] 2 [4.43, 15.50] 10 [-4.45, 4.45] 30.39, -23.41] [16.33, 20.47] 32 [-1.91, 5.15] [-6.53, 10.38] Mean Different M.Random, 9	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% CI -100 Favours [experimental] Favours [control] IV. Random, 95% CI Favours [experimental] Favours [control]
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Exhlasi2016 Famouri2016 Kobyliak2018 Kobyliak2018 Kobyliak2018 Kobyliak2019 Nabavi2014 Scorletti2020 Wiong2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Aller2011	188.7 = 19.27; C t: Z = 2.22 Mean 3 3 9 21.6 49.19 46.75 25.38 26.28 30.6 23.94 40 23.4 ² = 198.36; ct. Z = 0.45 Exp. Mean 121.1 24.2 25.28 26.2	68.9 hi [#] = 13: (P = 0.0: 50 11.6 1.8 12.2 11.32 9 10.44 4.5 5.4 Chi ² = 5.4 Chi ² = 6.6 (P = 0.6) Chi ² = 5.5 Chi ³ = 5	31 394 3.75, d 33) al <u>Total</u> 14 30 19 15 32 30 26 36 283 3513.42 36) tal <u>SD Tic</u> 3.4	149.7 f= 13 (P <u>Mean</u> 43.3 40 19.08 38.52 25.38 25.38 25.28 25.2 50.84 21.78 21.78 , df= 10 <u>stal</u>	 57 < 0.000 SD 8.9 7 6.3 8.17 9.18 8.64 9.84 5.4 1.8 (P < 0.0 Coo Mean 136.7 	32 386 101); I ^P = <u>Total</u> 14 29 16 15 32 28 32 24 36 4 10 270 000001); mtrol <u>SE</u> 38.5	1.2% 100.0% 90% Weight 8.7% 9.2% 9.3% 9.0% 9.2% 9.0% 9.2% 9.2% 9.2% 9.2% 100.0% P = 98% 100.0%	39.00 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0	[7.72, 70.28] 4 [0.47, 7.60] Difference indom, 95% CI 00 [-7.96, 7.36] 00 [-4.33, 2.33] 152 [-6.7, 7.36] 00 [-4.34, 2.33] 17 [3.24, 18.10] 12 [4.45, 4.45] 10 [-4.45, 4.45] 10 [-4.45, 4.45] 10 [-4.6, 10.34] 30.39, -23.41] 16.33, 20.47] 12 [-1.91, 5.15] [-6.53, 10.38] Mean Different M. Random, 9 1.5.10 [-49.71, 1	Favours [experimental] Favours [control] Mean Difference IV, Random, 95% CI -100 -50 0 50 1 Favours [experimental] Favours [control] Ce Mean Difference 15% CI IV, Random, 95% CI 19.51]
Shavakhi2013 Fotal (95% CI) Heterogeneity: Tau [#] Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Gramouri2016 Kobyliak 2018 Kobyliak 2019 Kobyliak 2018 Kobyliak 2018	188.7 = 19.27; C Expp Mean 43 39 21.6 49.19 46.75 26.38 26.28 30.6 23.94 40 23.4 = 198.36; ct. Z = 0.45 Exp Mean 121.1 93.3	68.9 hi [#] = 13: (P = 0.0: solution 11.6 6 1.8 12.2 11.32 9 10.44 9.18 4.14 4.5 5.4 Ch [#] = 5.4 Ch [#]	31 394 3.75, d 3.75, d 3.75, d 1.4 3.75, d 3.75, d 1.4 3.75, d 1.4 3.75, d 1.4 3.75, d 1.4 2.66, d 2.66, d 3.66, d 2.63, d 3.55, d 3.64, d 3.64, d 3.64, d 3.64, d 3.64, d 3.64, d 3.74,	149.7 (C Mean 43.3 40 19.08 25.38 25.38 25.28 21.6 21.78 21.78 (df = 10 (df = 10) (df	 57 < 0.000 Sontrol SD 8.9 7 6.3 8.9 7 6.3 8.9 8.4 8.64 1.8 8.64 1.8 9.84 5.4 1.8 (P < 0.1 Co Mean 136.7 02.93 	32 386 001); I [#] = Total 14 29 16 15 32 28 22 24 40 10 270 00001); 10 00001); 10 00001); 10 00001); 10 000000000000000000000000000000000	1.2% 100.0% 90% Weight 8.7% 9.2	39.00 4.0- Mean 7. Ra -0.3 -1.0 2.0 0.5 5.2 5.2%	[7.72, 70.28] 4 [0.47, 7.60] Difference mdom, 95% CI 30 [-7.96, 7.36] 30 [-4.33, 2.33] 2 [-0.67, 5.71] 7 [3.24, 18.10] 2 [4.65, 6.45] 30 [-4.45, 4.45] 30 [-4.65, 6.45] 30 [-4.65, 6.45] 30 [-4.65, 6.45] 30 [-4.65, 6.45] 30 [-4.65, 6.45] 30 [-4.65, 10.38] [-6.53, 10.38] Mean Differen V. Random, 3 -15.10 [-4.9.7], -9.33 [-22.69	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% CI -100 -50 0 50 1 Favours [experimental] Favours [control] Cece Mean Difference 5% CI V. Random, 95% CI 19.51]
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz02020 Chong2021 Exhlasi2016 Kobyliak2018 Kobyliak2018 Kobyliak2018 Scorletti2020 Wong2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021	188.7 = 19.27; C = 2.22 Exp Mean 33 39 21.6 49.19 46.75 25.38 26.28 30.6 23.94 40 23.4 = 198.36; ct: Z = 0.45 Exp Mean Mean 121.1 93.39 98.569	68.9 hi [#] = 13:3 (P = 0.0: 5D 11.6 1.8 12.2 11.32 11.32 11.32 11.4 4.5 5.4 Chi ² = 5.6 (P = 0.6 Chi ² = 5.6 (P = 0.6 3 - 5.6 Chi ² = 5.6 3 - 5.6 Chi ² = 5.6 3 - 5.6 3 - 5.6 Chi ² = 5.6 Chi ³ = 5.6 Chi ³ = 5.6 Chi ³ = 5.6 Chi ³ = 5.6 Ch	31 394 3.75, d 3.75, d 3.7	149.7 f= 13 (P <u>Mean</u> 43.3 36.53 25.38 25.38 25.38 25.38 25.38 21.78 21.78 , df = 10 <u>Mean</u> 14 11 19	 57 < 0.000 SD 8.9 7 6.3 8.17 7 6.3 8.17 10.21 8.64 9.84 5.4 1.8 64 5.4 1.8 (P < 0.1 (P < 0.1 102.1 126.7 	32 386 001); P = Total 14 49 9 16 15 32 28 22 24 36 44 40 00001); P = Total 14 P = Total 14 49 9 16 52 28 22 24 36 6 32 23 24 36 32 32 32 36 32 32 32 36 32 32 32 32 36 32 32 32 32 32 32 32 32 32 32	1.2% 100.0% 90% Weichtt 8.7% 9.2% 9.3% 9.2% 9.0% 9.2% 9.2% 100.0% Г= 98% 14 3 29 14 3 29 16 16	39.00 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0	[7.72, 70.28] 4 [0.47, 7.60] Difference indom, 95% CI 00 [-7.96, 7.36] 00 [-4.33, 2.33] 52 [-0.67, 5.71] 10 [-4.45, 4.45] 00 [-4.43, 15.50] 0 [-4.46, 10.34] 10 [-4.45, 4.45] 0 [-4.68, 6.45] 0 [-4.63, 2.0.47] 12 [-1.91, 5.15] [-6.53, 10.38] Mean Different N.Random, 9 -15.10 [4.9.71, -9.33 [-22.89] -2.32 [-23.08]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% CI
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Famouri2016 Kobyliak 2018 Kobyliak 2018 Kobyliak 2018 Scorletti2020 Wong2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016	188.7 = 19.27; C t Z = 2.22 Mean 40.3 39 21.6 49.19 46.75 25.38 26.28 30.6 23.94 40 23.4 = 198.36; ct: Z = 0.45 Exp Mean 121.1 93. 98.969 124.1	68.9 $P^{\mu} = 13.3$ $P^{\mu} = 0.03$ $P^{\mu} = 0.03$ P^{μ	31 394 3.75, d 3.75, d 3.75, d 3.75, d 3.75, d 3.75, d 14 3.0 19 26 26 26 26 26 26 26 26 26 26	149.7 (= 13 (P <u>Mean</u> 43.3 40 19.08 38.52 38.52 38.52 25.38 25.38 25.38 25.38 25.4 21.78 (df = 10) <u>tal</u> 14 10 11 11 15 11	57 57 500000 500000 500000 5000000 5000000 50000000 50000000 500000000 500000000 500000000 5000000000 5000000000 5000000000 50000000000 50000000000000 5000000000000000 50000000000000000 5000000000000000000000000000000000000	32 386 101); ≠= Total 14 29 16 15 22 24 44 10 270 00001); strol strol 38.9 28.8 270 00001); 1000000000000000000000000000000000000	1.2% 100.0% 90% Weight 8.7% 9.2% 9.3% 9.2% 9.1% 9.2% 9.3% 9.2% 100.0% F = 98% 100.0% 14 3.29 14 3.15	39.00 4.0 4.0 4.0 7 7 7 8 8 9 7 8 9 8 9 8 9 9 9 9 9 9 9 9	[7.72, 70.28] 4 [0.47, 7.60] Difference indom, 95% (CI) 30 [-7.96, 7.36] 30 [-7.96, 7.36] 30 [-4.33, 2.33] 32 [-0.67, 5.71] 30 [-4.34, 2.33] 52 [-0.67, 5.71] 30 [-4.65, 6.45] 0 [0.46, 10.34] 30.39, -23.41] 16.63, 20.47] 52 [-1.91, 5.15] 16.653, 10.38] Mean Different Mandom, 7. -9.33 [-22.69] 2.32 [-23.08, 7] -15.65 [-36.81]	Favours [experimental] Favours [control] Mean Difference N. Random, 95% CI -100 -50 0 50 1 Favours [experimental] Favours [control] Ce Mean Difference 5% CI IV. Random, 95% CI 19.511 4.03 27.72]
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Famouri2016 Kobyliak2019 Kobyliak2019 Kobyliak2019 Nabavi2014 Scorletti2020 Wong2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Ekhlasi2016 Famouri2016	188.7 = 19.27; C = 2.22 Expr 43 39 21.6 49.19 46.75 25.38 26.28 30.6 23.94 40 23.4 = 198.36; ct: Z = 0.45 Exq Mean 121.1 93.39 98.969 124.1 81.6;	68.9 hi [#] = 13: (P = 0.0: briment 5 11.6 6 1.8 12.2 11.32 9 9.18 4.14 4.5 4 Chi ² = 5 (P = 0.6 b c (P = 0.6) b c c c c c c c c	31 394 3.75, d 3.75, d 3.75, d 3.75, d 3.75, d 3.75, d 3.75, d 3.75, d 3.75, d 3.95, d 3.05, d 3.0	149.7 f= 13 (P C Mean 43.3 40.0 38.52 36.53 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 21.6 21.78 df = 10 df	 57 < 0.000 SD 8.9 7 6.3 8.17 10.21 8.28 9.18 8.64 9.84 5.4 1.8 (P < 0.0 Co Mean 136.7 Co Co Mean 136.7 7.8.31 	32 386 101); F = Total 14 29 16 15 32 28 22 24 36 32 224 36 410 00001); mtrol <u>SI</u> 38,6 37,1138 28 270 00001); 12,99 37,1138 12,99 16,99 10,99	1.2% 100.0% 90% Weicht 8.7% 9.3% 9.3% 9.3% 9.3% 9.3% 9.2% 9.2% 100.0% 100.0% 1 4 1 4 1 14 1 16 1 16 3 15 3 3 22	39.00 4.0 4.0 4.0 4.0 7.0 4.0 4.0 7.0 7.0 10.0 10.0 10.0 10.0 10.0 10.0	[7.72, 70.28] 4 [0.47, 7.60] Difference indom, 95% CI 00 [-7.96, 7.36] 00 [-4.33, 2.33] 52 [-0.67, 5.71] 10 [-4.45, 4.45] 00 [-4.45, 4.45] 00 [-4.65, 6.45] 00 [-4.65, 6.45] 00 [-4.65, 1.038] [-6.53, 10.38] [-6.53, 10.38] [-5.5] [-5.27, 1.038] [-5.65 [-5.84]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% CI -100 Favours [experimental] Favours [control] IV. Random, 95% CI Favours [experimental] Favours [control] IV. Random, 95% CI Favours [experimental] Favours [control]
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Famouri2016 Kobyliak 2018 Kobyliak 2018 Kobyliak 2018 Nabavi2014 Scorletti2020 Wiong2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Aller201 Behrouz2020 Chong2021 Ekhlasi2016 Famouri2016 Famouri2016 Famouri2016 Famouri2016 Famouri2016 Famouri2016 Famouri2016	188.7 = 19.27; C t: Z = 2.22 Mean 3 3 9 21.6 49.19 46.75 25.38 26.28 30.6 23.94 40 23.4 ² = 198.36; ct: Z = 0.45 Exp Mean 121.1 93.39 98.9699 124.1 93.898.969 124.1 93.898.969 124.1 93.898.969 124.1 93.898.969 124.1 93.898.969 124.1 93.898.969 124.1 132.603 124.1 132.603 124.1 125.	68.9 $hi^{\mu} = 13.3$ (P = 0.03) 11.6 6 1.8 12.2 11.32 12.2 11.32 12.2 11.32 12.2 11.32 12.2 12.3 12.2 12.3 12.2	31 394 3.75, d 3) al Total 14 30 19 15 32 26 26 26 26 26 26 26 26 26 2	149.7 (= 13 (P Mean 43.3 40 19.08 25.28 25.28 25.28 25.38 25.2 21.6 21.78 , df = 10	 57 50,000 50 50 7 6.3 7 7 6.3 8.64 8.64 9.18 8.64 9.18 8.64 9.18 8.64 1.8 7 7 10.21 1.21 1.	32 386 001); F = Total 14 29 16 15 32 28 8 22 24 36 270 00001); 00001); 00001); 10001; 100001; 10000; 1000; 10000; 1000; 1000; 1000; 1000; 1000; 1000; 10	1.2% 100.0% 90% Weight 8.7% 9.2% 9.3% 9.0% 9.2% 9.3% 9.2% 9.3% 9.2% 100.0% P=98% 14 3 14 3 29 16 16 16 16 16 22 2 28	39.00 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0	IP, 72, 70, 28] 4 [0.47, 7.60] Difference Indom, 95% CI 00 [7.96, 7.36] 00 [4.33, 2.33] 152 [-0.67, 5.71] 17 [3.24, 18.10] 2 [4.94, 15.50] 10 [4.45, 4.45] 10 [-4.6, 10.34] 30.39, -23.41] 16.33, 20.47] 12 [-1.91, 5.15] [-6.53, 10.38] Mean Differen V.Random, 9 -15.10 [-4.97, 1, -9.33 [-22.69] -33 [-23.68] -3.34 [-5.65] -16.6 [-3.44]	Favours [experimental] Favours [control] Mean Difference IV, Random, 95% CI -100 -50 0 50 1 Favours [experimental] Favours [control] Ce Mean Difference IV, Random, 95% CI Favours [experimental] Favours [control]
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Famouri2016 Kobyliak2018 Kobyliak2018 Scorletti2020 Wong2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Famouri2016 Famouri2016 Famouri2016 Famouri2016 Famouri2016 Famouri2018	188.7 = 19.27; C = 2.22 Exp Mean 43 39 21.6 49.19 46.75 25.38 26.28 30.6 23.94 40 23.4 = 198.36; ct. Z = 0.45 Exp Mean 121. 93.3 9.8969 124.11 81.6 132.603 125.64	68.9 hi [#] = 13: (P = 0.0: simment so 11.6 6 8 12.2 11.32 9 10.44 4.5 5.4 Chi ² = 5 (P = 0.6 (P = 0.6 Chi ² = 5 (P = 0.6 Chi ² =	31 394 3.75, d 3) al Total 14 30 26 26 26 26 26 26 26 26 26 26	149.7 (= 13 (P (C Mean) 43.3 40.0 38.52 36.53 25.38 25.26 25.38 25.38 25.26 25.38 25.26 25.88 25.26 25.88 25.26 25.2	57 57 50 50 50 50 50 50 50 50 50 50 50 50 50	32 386 101); F = Total 14 29 16 15 22 28 22 24 36 15 22 24 30 00001); mtrol 270 00001); 38.6 38.6 38.6 38.6 14.7	1.2% 100.0% 90% Weight 8.7% 9.2% 9.3% 9.2% 9.3% 9.2	39.00 4.0 4.0 4.0 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	[7.72, 70.28] 4 [0.47, 7.60] Difference mdom, 95% CI 30 [-7.96, 7.36] 30 [-4.33, 2.33] 2 [-0.67, 5.71] 7 [3.24, 18.10] 2 [4.65, 6.45] 30.39, -23.41] [16.33, 20.47] 32 [-1.91, 5.15] [-6.53, 10.38] Mean Differen M.Random, 9 -15.10 [-49.71, -5.15] -16.65 [-35.61] -3.34 [-5.95, -1.16 [-3.44] -3.34 [-5.95, -1.16 [-3.44] -16.65 [-36.81] -3.34 [-5.95, -1.16 [-3.24]	Favours [experimental] Favours [control] Mean Difference IV. Random, 95% CI -100 -50 0 50 1 Favours [experimental] Favours [control] rece Mean Difference 5% CI IV. Random, 95% CI 19.51] 4.03 27.72] 4.03 5.76]
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Famouri2016 Kobyliak2018 Kobyliak2019 Nabavi2014 Scorletti2020 Wong2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Aller2011 Behrouz2020 Chong2021 Ekhlasi2016 Kobyliak2018 Kobyliak2018 Kobyliak2018	188.7 = 19.27; C t: Z = 2.22 Mean 39 21.6 49.19 46.75 25.38 30.6 23.94 40 23.4 = 198.36; ct: Z = 0.45 Exg Mean 121.1 93.9 99.969 124.1 81.6 132.603 125.64 131.830	68.9 $hi^{\mu} = 133$ SD 11.6 6 1.8 12.2 9 10.44 9.18 4.14 4.5 5.4 $Chi^{\mu} = 5.4$ $Chi^{\mu} = 5.4$ $Chi^{\mu} = 5.2$ 3.2 3.2 5.2 3.2 5.2 3.3 5.2 3.3 5.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3.3 5.3 3	31 394 3.75, d 3) al Total 14 30 19 15 32 26 6 26 45 10 283 3513.42 283 37 34.9 888 32 283 37 32 283 37 32 32 37 37 37 37 37 37 37 37 37 37	149.7 (= 13 (P (C Mean 43.3 40.3 19.08 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 25.38 21.6 21.78 , df = 10 () () () () () () () () () ()	 57 < 0.000 sontrol 80 8.9 7 6.3 8.17 10.21 8.64 9.18 8.64 9.18 8.64 9.18 5.4 1.8 (P < 0.1 0.16 0.23 0.65 0.574 	32 386 001); F = Total 14 29 16 15 32 28 22 24 36 32 22 24 10 270 00001); 10 38.9 38.9 38.5 37.1133 14.75 14.75 14.75 10 10 10 10 10 10 10 10 10 10	1.2% 100.0% 90% Weight 8.7% 9.2% 9.3% 9.2% 9.0% 9.2% 9.0% 9.2% 100.0% P=98% 100.0% P=98% 148 2.28 1.53 2.22 2.24	39.00 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0	IP, 72, 70, 28] 4 [0.47, 7.60] Difference Indom, 95% CI 00 [-7.96, 7.36] 00 [-4.33, 2.33] 12 [-6.7, 5.71] 10 [-4.45, 4.45] 10 [-4.45, 4.45] 10 [-4.45, 4.45] 10 [-4.45, 4.45] 10 [-4.45, 4.45] 10 [-4.65, 6.45] 10 [-4.65, 1.34] [16.33, 20.47] 12 [-1.91, 5.15] [-6.53, 10.38] Mean Different N.Random, 9 -15.10 [-49.71, -9.33 [-22.69] -2.32 [-2.308, 3.34 [-5.95, 1.16 [-3.44] -2.32 [-5.73, 0.77 [-2.54]	Favours [experimental] Favours [control] Mean Difference IV, Random, 95% CI -100 Favours [experimental] Favours [control] Ce Mean Difference 5% CI IV, Random, 95% CI I (10) Favours [experimental] Favours [control] Ce Mean Difference 5% CI I (10) Favours [experimental] Favours [control] Ce Mean Difference 5% CI I (10) Favours [experimental] Favours [control] Ce Mean Difference 5% CI I (10) Favours [experimental] Favours [control]
Shavakhi2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effec Study of Subgroup Aller2011 Behrouz2020 Chong2021 Exhlasi2016 Farnouri2016 Kobyliak2018 Kobyliak2018 Kobyliak2018 Kobyliak2019 Nabavi2014 Scorletti2020 Wong2013 Total (95% CI) Heterogeneity: Tau ² Test for overall effect Study of Subgroup Aller2011 Behrouz2020 Chong2021 Exhlasi2016 Farnouri2016 Farnouri2016 Farnouri2016 Farnouri2018 Kobyliak2018 Kobyliak2018	188.7 = 19.27; C t: Z = 2.22 Mean 40.3 39 21.6 49.19 46.75 25.38 26.28 30.6 23.94 40 23.4 = 198.36; ct: Z = 0.45 Exp Mean 121.1 93.98 98.969 124.1 81.6 132.664 131.830 99.88	68.9 $P^{\mu} = 13:$ $P^{\mu} = 0.0:$ $P^{\mu} = 0.0:$ P^{μ}	31 394 3.75, d 1 1 1 1 1 1 3 3 3 3 3 3 3 3 3 3 3 3 3	149.7 (= 13 (P Mean 43.3 40 19.08 25.38 25.38 25.38 25.38 25.4 21.78 (df = 10) (df = 10) (df = 10) (df = 10) (df = 12) 26 121 26 121 27 121 28 52 28 52	57 57 500000 500000 500000 5000000 50000000 50000000 500000000 5000000000 50000000000 500000000000000 50000000000000000 5000000000000000000000000000000000000	32 386 001); ≠= Total 14 29 16 15 32 22 24 44 15 32 22 24 44 10 270 00001); 14,77 38,6 37,113 26,94 0.4382,326,94	1.2% 100.0% 90% Weight 8.7% 9.2	39.00 4.0 4.0 4.0 3.0 3.0 4.0 4.0 4.0 5.0 5.4 5.2 5.4 1.8.40 1.8 1.8 40 1.8 1.93 4.0 3.0 5.4 1.93 4.0 5.4 5.2 5.2 5.2 5.2 5.2 5.2 5.2 5.2 5.2 5.2	[7.72, 70.28] 4 [0.47, 7.60] Difference indom, 95% CI 30 [-7.96, 7.36] 0 [-4.33, 2.33] 32 [-6.67, 5.71] 10 [-4.45, 4.45] 10 [-4.45, 4.45] 10 [-4.64, 10.34] 30.39, -23.41] 16.33, 20.47] 32 [-1.91, 5.15] 16.653, 10.38] Mean Different N.Random, 7 -15.40 [-4.63, 44 -3.34 [-5.95, 13] -15.65 [-53.81 -3.34 [-5.93, 1.16 [-53.41 -3.34 [-5.94, -10.20 [-21.52	Favours [experimental] Favours [control] Mean Difference N. Random, 95% CI -100 -50 0 50 1 Favours [experimental] Favours [control] Ce Mean Difference 5% CI N. Random, 95% CI 10511 4.03 27.72] 27.72 27
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Figure 8. The blood lipid levels. A total of 12 studies reported changes in TC levels from baseline (A): the analysis showed that TC levels were significantly reduced after probiotic intervention. A total of 15 studies reported changes in TG compared to pre-baseline (B): the analysis showed that TG levels were significantly reduced after probiotic intervention. A total of 11 studies reported changes in HDL-C from baseline (C): the analysis showed that HDL-C levels were elevated after probiotic intervention. A total of 11 studies reported changes in LDL-C from baseline (D): the analysis showed that after probiotic intervention, LDL-C was elevated. TC = total cholesterol, TG = triglyceride.

role in regulating immunity and energy metabolism. When the intestinal flora is unbalanced, the tight junction of the intestine is destroyed, and the products in the intestine enter the liver through the portal vein, which will activate downstream toxicity and related inflammatory responses, and disorder of lipid metabolism, eventually leading to the occurrence of nonalcoholic fatty liver disease.^[45]

Probiotics contain a variety of beneficial bacteria that can restore the intestinal flora and are now being tried to improve the development of nonalcoholic liver disease, intervene in fat metabolism by regulating the intestinal flora and restoring the stability of the intestinal ecology, improve liver function, reduce liver inflammation, etc. At present, there are many studies on probiotic preparations. Different probiotic preparations will have different effects on the results under different intervention courses and intervention doses. This study systematically reviewed the efficacy and safety of probiotics in the treatment of nonalcoholic fatty liver disease, with a total of 21 studies

Α	Ехр	erimen	tal	с	ontrol			Mean Difference	Mean D	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Rando	m, 95% Cl	
Ahn 2019	1.22	1.05	30	1.64	1.17	35	20.4%	-0.42 [-0.96, 0.12]			
Aller2011	1.21	1.65	14	1.03	1.11	14	18.3%	0.18 [-0.86, 1.22]		•	
Bomhof2018	141.4	107.3	19	100.6	74.7	20	0.0%	40.80 [-17.51, 99.11]			
Duseja2019	13.31	3.28	30	12.11	6.35	28	10.5%	1.20 [-1.43, 3.83]		+	
Kobyliak2018	14.03	2.61	26	9.18	3.14	22	15.2%	4.85 [3.20, 6.50]		•	
Kobyliak 2018	14.17	3.87	26	10.94	2.1	24	14.9%	3.23 [1.52, 4.94]		-	
Kobyliak2019	1.27	0.6	8	0.77	0.2	5	20.6%	0.50 [0.05, 0.95]		† -	
Total (95% CI)			153			148	100.0%	1.41 [0.21, 2.61])	
Heterogeneity: Tau ² =	= 1.77; C	hi ² = 49	.83, df	= 6 (P <	0.000	01); I ² =	88%		100		100
Test for overall effect			•						-100 -50 Favours (experimental)	0 50 Favours (control)	100

В

	Exp	eriment	al	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Ahn 2019	6.99	2.92	30	6.99	5.79	35	13.1%	0.00 [-2.18, 2.18]	+
Aller2011	9.8	2.13	14	8.8	1.19	14	21.7%	1.00 [-0.28, 2.28]	•
Bomhof2018	1.43	0.23	8	1.64	0.15	5	32.7%	-0.21 [-0.42, -0.00]	•
Duseja2019	107.8	94.4	19	243.15	167.1	20	0.0%	-135.35 [-220.00, -50.70]	←
Kobyliak2018	43.65	12.19	30	48.2	7.87	28	3.4%	-4.55 [-9.80, 0.70]	
Kobyliak 2018	42.31	11.79	26	44.97	11.32	22	2.2%	-2.66 [-9.21, 3.89]	-+
Kobyliak2019	44.82	12.62	26	48.17	8.83	24	2.6%	-3.35 [-9.35, 2.65]	
Vajro2011	10.71	1.81	31	10.99	2.5	32	24.2%	-0.28 [-1.36, 0.80]	1
Total (95% CI)			184			180	100.0%	-0.24 [-1.25, 0.78]	
Heterogeneity: Tau ² =	= 0.81; C	hi² = 17	48, df :	= 7 (P = 0	.01); F=	= 60%			
Test for overall effect				1000					-100 -50 0 50 100 Favours [experimental] Favours [control]

	Expe	rimen	tal	C	ontrol			Mean Difference		Mean	Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Rar	ndom, 95% Cl	<u>í</u>	
Ahn 2019	0.35	0.15	30	0.2	0.3	35	32.3%	0.15 [0.04, 0.26]					
Bomhof2018	8.03	0.8	8	12.86	1.89	5	2.2%	-4.83 [-6.58, -3.08]			-		
Duseja2019	0.15	0.16	19	0.41	0.27	20	31.4%	-0.26 [-0.40, -0.12]					
Scorletti2020	0.11	0.1	45	0.15	0.1	44	34.1%	-0.04 [-0.08, 0.00]			· •		
Total (95% CI)			102			104	100.0%	-0.15 [-0.42, 0.11]					
Heterogeneity: Tau ² =	= 0.05; C	hi ² = 4	9.43, dt	f= 3 (P <	< 0.000	001); F	= 94%		100	50	-		4.00
Test for overall effect	Z=1.12	(P = 0	0.26)						-100 Favour	-50 s (experiment	al] Favours	50 [control]	100

D Mean Difference Mean Difference Experimental Control Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% Cl Asgharian2016 0.24 30 0.99 0.1 38.8% 0.42 [0.33, 0.51] 1.41 35 Behrouz2020 6.3 4.99 30 6.94 3.75 29 17.0% -0.64 [-2.89, 1.61] Chong2021 3.9 6.1 19 2.7 2.7 16 11.6% 1.20 [-1.85, 4.25] Eslamparast2014 -1.28 [-2.14, -0.42] 1.93 26 3.21 1.9 32.7% 1.2 26 Total (95% CI) 105 106 100.0% -0.23 [-1.46, 1.01] Heterogeneity: Tau² = 1.02; Chi² = 15.80, df = 3 (P = 0.001); l² = 81% -100 -50 50 100 Test for overall effect: Z = 0.36 (P = 0.72) Favours [experimental] Favours [control]

Figure 9. The inflammatory factors levels. A total of 7 studies reported changes in IL-6 from baseline (A): the analysis showed that IL-6 was elevated after probiotic intervention. A total of 8 studies reported changes in TNF- α from baseline (B): the analysis showed that after probiotic intervention, TNF- α decreased. A total of 4 studies reported changes in LPS from baseline (C): the analysis showed that LPS was reduced after probiotic intervention. A total of 4 studies reported changes in CRP compared to baseline (D): The analysis showed that after probiotic intervention, h-CRP was elevated. h-CRP = C-reactive protein, IL-6 = interleukin- 6, LPS = lipopolysaccharides, TNF- α = tumor necrosis factor- α .

involving 1037 participants. The results of our meta-analysis showed that after probiotic intervention, the liver function (ALT, AST, GGT) of patients was significantly improved, and the results were statistically significant, which was consistent with the results of previous studies.^[46-49] In addition, our study shows that probiotic treatment can effectively improve steatosis, reduce blood sugar, insulin, etc. Although insulin resistance is reduced, the results are not statistically significant, which is partially different from previous studies such as Khan.^[48] In the results of this meta-analysis, there was no statistical significance in insulin resistance and blood sugar. They included 7 studies on blood sugar, while we included 11 studies. After excluding the heterogeneity source literature, a total of 10 studies were included, but no results obtained were significantly changed. After reducing heterogeneity, our study showed that probiotics had a significant regulatory effect on TG and TC, but no significant improvement in HDL-C and LDL-C. In addition, our study found that probiotics did not significantly improve inflammatory factors, such as TNF- α , IL-6, LPS, h-CRP, etc., which is consistent with the results of previous studies.^[48,49] In our research, we found that probiotics did not reduce BMI and total fat mass.

In order to determine the safety of probiotic preparations, we reported adverse reaction outcomes in our study, and the results showed that probiotic preparations had more gastrointestinal effects, but no serious adverse reactions. In addition, we

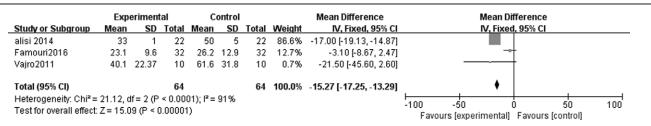


Figure 10. The ALT levels in children. A total of 3 studies reported the efficacy of probiotics in the treatment of children with NAFLD, but only ALT levels met the criteria for meta-analysis. The analysis results showed that after probiotic intervention, the ALT level in the children group was significantly improved. ALT = alanine aminotransferase, NAFLD = nonalcoholic fatty liver disease.

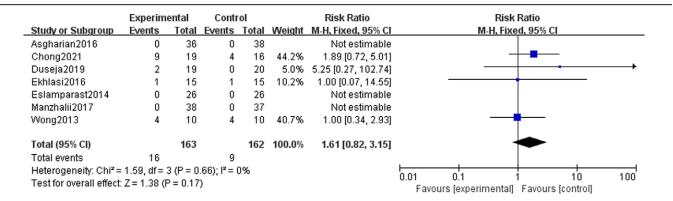


Figure 11. The Adverse Reactions. A total of 7 studies explicitly reported adverse reactions: the analysis showed that the incidence of adverse reactions was higher in the probiotic therapy group than in the placebo group.

conducted an independent meta-analysis of probiotics on children with nonalcoholic fatty liver disease. The results showed that probiotics had a good effect on improving ALT in children, and related reports clearly mentioned that no adverse reactions occurred, indicating that probiotics bacteria can be used as a safe and effective intervention for the treatment of children with nonalcoholic fatty liver disease.

In the study, we found that when the course of probiotics was longer than 12 weeks, the improvement of ALT, GGT, TG, blood sugar and blood sugar was better. This result provides a scientific basis for probiotics as a long-term intervention in the treatment of nonalcoholic fatty liver disease. And less than 12 weeks is more effective for reducing BMI.

In this study, we included studies from different countries and regions. And we found some differences in these countries and regions. On the one hand, for Italy, Denmark, Spain and other countries with the Mediterranean diet, according to some studies, the Mediterranean diet contains a lot of fiber and polyphenols, which can reduce the proportion of E. coli, increase the abundance of bifidobacterium, and help to improve the composition of the SCFA.^[50,51] On the other hand, for countries with a traditional western diet (butter, red meat and other high fat food) like Britain, Ukraine, and Canada, such a high fat diet can increase intestinal permeability, which causes inflammation and metabolic related disease. With this research, Britain began to advocate eating more fruits and vegetables containing polyphenols so that it could reduce the risk of metabolic diseases and heart cerebrovascular disease.^[52,53] Regrettably, only 3 studies in the included studies reported the regulating effect of probiotics on intestinal flora, but because the indicators could not be effectively quantified and unified, they were not included in the meta-analysis. At the same time, since the gut microbiota is affected by dietary habits, studies in different regions may lead to biases in the biological characteristics of the gut microbiota. It is hoped that in the future reports of randomized clinical studies, the outcome indicators of intestinal flora can be reported, and the dietary patterns of relevant regions can be clarified.

5. Conclusion

This study comprehensively evaluated the related outcome indicators of probiotics in the treatment of nonalcoholic fatty liver disease. Compared with previously published studies, we included more outcome indicators for comprehensive analysis and evaluation, which further improved the probiotics in the treatment of nonalcoholic fatty liver disease. Efficacy and safety of alcoholic liver disease, and a systematic review and analysis of the efficacy and safety reported in pediatric patients. The findings suggest that it is feasible that probiotics can treat nonalcoholic liver disease. Several strains of Lactobacillus and Bifidobacterium are able to compete with and displace pathogenic bacteria. Therefore, probiotics may improve the intestinal ecology and microbial composition, compete with and replace pathogenic bacteria, and prevent the small intestinal bacteria overgrowth. With the incidence of NAFLD rising, it is still crucial to find out therapeutic methods to alleviate the occurrence and progression of NAFLD. A growing number of studies have expanded our understanding of the mechanisms by which gut microbes, especially beneficial bacteria, affect NAFLD. However, further well-designed prospective clinical studies incorporating preclinical models are needed to identify pathogenic microorganism-host interactions in the pathogenesis and development of NAFLD.

Author contributions

The research design, thesis writing and revision were completed by XZ, JW, SZ, and other researchers. XZ was responsible for the literature retrieval of the database. Statistical analysis and literature screening were independently completed by JL and ZY. The literature quality assessment process was independently completed by JW and LM. The proofreading work was done by SZ and JW.

Conceptualization: Xiangyu Zhou.

Data curation: Xiangyu Zhou, Zuoyu Ye, Leiming Mao.

Study or Subgroup									
	Exper Mean	rimental SD T			ntrol SD	<u>Fotal</u>	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% Cl
sgharian2016	26.88 49	4.28 26	36 19	35.07 51	4.35	38 16	0.0%	-8.19 [-10.16, -6.22]	
hong2021 khlasi2016		6.54			9.42	15	11.9%	-2.00 [-21.56, 17.56] 6.46 [0.66, 12.26]	-
avadi2017		14.12	19		2.74	20	7.3%	10.12 [1.67, 18.57]	- - -
obyliak2018		11.14			6.36	28	14.9%	1.50 [-3.13, 6.13]	t
obyliak 2018		4.62			1.91	22	23.7%	1.64 [-0.31, 3.59]	L
obyliak2019 obyvi2014	36.3 2 24.5	22.87 1.64	26 36	29.26 25.5	3.82 2.1	24 36	6.7% 0.0%	7.04 [-1.88, 15.96]	
abavi2014 airo2011		31.8	10		2.37	10	1.2%	-1.00 [-1.87, -0.13] 21.50 [-2.60, 45.60]	<u> </u>
ubtotal (95% CI)	01.0		145	40.1 2	2.01	135	67.5%	3.97 [0.97, 6.97]	•
eterogeneity: Tau ² =				(P = 0.1	5); I² =	36%			
est for overall effect:	Z = 2.59 (P = 0.01	0)						
2.1.2 ALT>12									
n 2019	38.8	35	30	44.5	23	35	3.0%	-5.70 [-20.36, 8.96]	
isi 2014	33	1	22	50	5	22		-17.00 [-19.13, -14.87]	
ler2011		30.4	14		35.5	14	1.1%	-4.40 [-28.88, 20.08]	
ehrouz2020		9.25	30		0.25	29	4.5%	-8.00 [-19.50, 3.50]	
omhof2018	68.1	14	8		14.2	5	2.6%	8.80 [-6.98, 24.58]	
useja2019 slamparast2014	45.1 64.17	29.7 11.1	19 26	68 44.2	40.7 3.8	20 26	1.4% 0.0%	-22.90 [-45.18, -0.62]	
amouri2016		12.9	32	23.1	3.0 9.6	32	12.4%	19.97 [15.46, 24.48] 3.10 [-2.47, 8.67]	-
anzhalii2017	50.42 1		38		2.74	37	0.0%	10.12 [4.04, 16.20]	
orletti2020		30.72	45	57	35	44	3.3%	-1.62 [-15.31, 12.07]	-+-
havakhi2013	112.5	68.7	31		32.5	32	0.0%	67.30 [40.62, 93.98]	
ong2013	70	16	10	74	11	10	4.2%	-4.00 [-16.03, 8.03]	
ubtotal (95% CI) eterogeneity: Tau ² =	13.63; Cł		188 8, df =	7 (P = 0.	23) <u>;</u> I² =	189 : 25%	32.5%	-1.99 [-7.19, 3.20]	٦
est for overall effect.									
otal (95% CI)			333				100.0%	2.31 [-0.36, 4.99]	•
eterogeneity: Tau ^z =				14 (P = (0.10); I ^z	= 33%	•		-100 -50 0 50 100
est for overall effect:) est for subaroup diffe				= 1 /P	0.065.5	R= 724	296		Favours [experimental] Favours [control]
estion suburdub diffe	erences: (um ⁻ ≓ 3.	. เฮ. ตไ	- i (P'≓	v.us). ľ	- 73.1	2.70		
	E. de ou	rimenta			ntrol	T-1-1		Mean Difference	Mean Difference
tudy or Subgroup	Mean	SD T	otal	Mean	SD	rotal	Weight	IV, Random, 95% C	CI IV, Random, 95% CI
3.1.1 AST <12 sqharian2016	23.67	1.73	36	29.03	2.08	38	61.9%	-5.36 [-6.23, -4.49	aı 🗖
hong2021	23.67	20	36 19	29.03 49	2.08	38 16	01.9%	-11.00 (-26.59, 4.59	
khlasi2016		13.4		34.54	6.8	15	0.8%	-4.02 [-11.62, 3.58	
avadi2017		9.08	19		12.46	20	1.0%	-10.48 [-17.30, -3.66	
obyliak2018	32.98	8.39	30	41.3	6.45	28	3.2%	-8.32 [-12.16, -4.48	8]
obyliak 2018	25.72	3.6		31.08	0.77	22	23.2%	-5.36 [-6.78, -3.94	4] •
obyliak2019		7.06	26	36.84	4.28	24	4.5%	-6.84 [-10.05, -3.63	
labavi2014 ubtotal (95% CI)	27.5		36	25	0.41	36	0.0%	2.50 [0.66, 4.34	
ubtotal (95% Cl) leterogeneity: Tau² =	= 0.00: Ch		171 0. df=	6 (P = 0	48): I ²	163 = 0%	94.8%	-5.58 [-6.29, -4.88	a '
est for overall effect:						2.00			
3.1.2 AST >12	00 F	22	20	24.7	20.5	~	0.00	0.001/1.00.0000	
ihn 2019 Iller2011	32.5 35.6	22 10.4	30 14	31.7 36.4	28.5 13.8	35 14	0.3%	0.80 [-11.49, 13.09	
aler2011 Sehrouz2020		10.4 5.75	14 30		13.8	14 29	1.3%	-0.80 [-9.85, 8.25 -8.00 [-13.92, -2.08	
)useja2019		5.75 16.4	19	44.9	18.5	29	0.4%	-8.90 [-19.86, 2.06	
slamparast2014		2.7	26	60.34	13.1	26	0.0%		
	35.1	4.1							
	35.1 24.3	7.7	32	26.6	11.8	32	2.0%	-2.30 [-7.18, 2.58	8] —†
amouri2016 anzhalii2017	24.3 32.7	7.7 2.4	32 38	47.6	3.2	37	0.0%	-14.90 [-16.18, -13.62	2]
amouri2016 anzhalii2017 corletti2020	24.3 32.7 34	7.7 2.4 16.8	32 38 45	47.6 40.8	3.2 24	37 44	0.0%	-14.90 [-16.18, -13.62 -6.80 [-15.42, 1.82	2]
amouri2016 anzhalii2017 corletti2020 havakhi2013	24.3 32.7 34 44.2	7.7 2.4 16.8 33.9	32 38 45 31	47.6 40.8 113.4	3.2 24 71	37 44 32	0.0% 0.6% 0.0%	-14.90 [-16.18, -13.62 -6.80 [-15.42, 1.82 -69.20 [-96.54, -41.86	2] 2] 6]
amouri2016 anzhalii2017 corletti2020 havakhi2013 /ong2013	24.3 32.7 34	7.7 2.4 16.8 33.9 6	32 38 45 31 10	47.6 40.8	3.2 24	37 44 32 10	0.0% 0.6% 0.0% 0.0%	-14.90 [-16.18, -13.62 -6.80 [-15.42, 1.82 -69.20 [-96.54, -41.86 22.00 [10.83, 33.17	2] 2] 6] 7]
amouri2016 anzhalii2017 corletti2020 havakhi2013 long2013 ubtotal (95% CI)	24.3 32.7 34 44.2 37	7.7 2.4 16.8 33.9 6	32 38 45 31 10 170	47.6 40.8 113.4 15	3.2 24 71 17	37 44 32 10 174	0.0% 0.6% 0.0%	-14.90 [-16.18, -13.62 -6.80 [-15.42, 1.82 -69.20 [-96.54, -41.86 22.00 [10.83, 33.17	2] 2] 6] 7]
amouri2016 anzhalii2017 corletti2020 havakhi2013 (ong2013 ubtotal (95% CI) eterogeneity: Tau ² =	24.3 32.7 34 44.2 37 = 0.00; Ch	7.7 2.4 16.8 33.9 6	32 38 45 31 10 170 7, df =	47.6 40.8 113.4 15	3.2 24 71 17	37 44 32 10 174	0.0% 0.6% 0.0% 0.0%	-14.90 [-16.18, -13.62 -6.80 [-15.42, 1.82 -69.20 [-96.54, -41.86 22.00 [10.83, 33.17	2] 2] 6] 7]
amouri2016 lanzhalii2017 icorletti2020 havakhi2013 Vong2013 ubtotal (95% CI) leterogeneity: Tau ² = est for overall effect:	24.3 32.7 34 44.2 37 = 0.00; Ch	7.7 2.4 16.8 33.9 6 ni ² = 4.37 (P = 0.0	32 38 45 31 10 170 7, df =	47.6 40.8 113.4 15	3.2 24 71 17	37 44 32 10 174 = 0%	0.0% 0.6% 0.0% 0.0%	-14.90 [-16.18, -13.62 -6.80 [-15.42, 1.82 -69.20 [-96.54, -41.86 22.00 [10.83, 33.17	20 21 71 71 50 ◆
amouri2016 Ianzhali2017 icorletti2020 ishavakhi2013 Vong2013 iubtotal (95% CI) Ieterogeneity: Tau ^e = 'est for overall effect: otal (95% CI) Ieterogeneity: Tau ^e =	24.3 32.7 34 44.2 37 = 0.00; Ch t: Z = 2.91	7.7 2.4 16.8 33.9 6 hi ² = 4.37 (P = 0.0	32 38 45 31 10 170 7, df = 104) 341 39, df	47.6 40.8 113.4 15 5 (P = 0.	3.2 24 71 17 50); I ²	37 44 32 10 174 = 0% 337	0.0% 0.6% 0.0% 5.2% 100.0%	-14.90 [-16.18, -13.62 -6.80 [-15.42, 1.82 -69.20 [-96.54, -41.96 22.00 [10.83, 33.17 -4.45 [-7.45, -1.45	2] 2] 7] 5]
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amouri2016 Ianzhali2017 icorletti2020 ishavakhi2013 Vong2013 iubtotal (95% CI) Ieterogeneity: Tau ^e = 'est for overall effect: otal (95% CI) Ieterogeneity: Tau ^e =	24.3 32.7 34 44.2 37 = 0.00; Ch : Z = 2.91 = 0.00; Ch : Z = 15.83	7.7 2.4 16.8 33.9 6 $hi^2 = 4.37$ (P = 0.0 $hi^2 = 10.3$ 3 $(P < 0.1)$	32 38 45 31 10 170 7, df = 104) 341 39, df .0000	47.6 40.8 113.4 15 5 (P = 0. = 12 (P = 1)	3.2 24 71 17 50); I ² 0.58);	37 44 32 10 174 = 0% 337 ² = 09	0.0% 0.6% 0.0% 5.2% 100.0%	-14.90 [-16.18, -13.62 -6.80 [-15.42, 1.82 -69.20 [-96.54, -41.96 22.00 [10.83, 33.17 -4.45 [-7.45, -1.45	21 21 51 51 11 1100 -500 0 50 100
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amouri2016 lanzhaili2017 contetti2020 havakhi2013 (org2013 ubtotal (95% CL) leterogeneity: Tau ² = est for overail effect: otal (95% CL) leterogeneity: Tau ² = est for overail effect est for suboroup diff	24.3 32.7 34 44.2 37 = 0.00; Ch : Z = 2.91 = 0.00; Ch : Z = 15.8; fferences:	7.7 2.4 16.8 33.9 6 $hi^2 = 4.37$ (P = 0.0 $hi^2 = 10.3$ 3 $(P < 0.1)$	32 38 45 31 10 7, df = 104) 341 39, df 0.52. d	47.6 40.8 113.4 15 5 (P = 0. = 12 (P = 1)	3.2 24 71 17 50); I ² 0.58);	37 44 32 10 174 = 0% 337 1 ² = 0?	0.0% 0.6% 0.0% 5.2% 100.0%	-14.90 [-16.18, -13.62 -6.80 [-15.42, 1.82 -69.20 [-96.54, -41.96 22.00 [10.83, 33.17 -4.45 [-7.45, -1.45	2] 2] 7] 5] • • • • • • • • • • • • • • • • • • •
amouri2016 ambalii2017 corletii2020 havakhi2013 (ong2013 ubtotal (95% C) eterogeneity: Tau ² = stifor overall effect satif or overall effect set for overall effect set for subaroup diff	24.3 32.7 34 44.2 37 = 0.00; Ch : Z = 2.91 = 0.00; Ch : Z = 15.8; fferences:	7.7 2.4 16.8 33.9 6 $hi^{2} = 4.37$ (P = 0.0 $hi^{2} = 10.3$ 3 (P < 0. : Chi ² = 0	32 38 45 31 10 170 7, df = 104) 341 39, df 0.52. df 0.52. df	47.6 40.8 113.4 15 5 (P = 0. = 12 (P = 1)	3.2 24 71 17 50); I ² : 0.58); = 0.47) Contr	37 44 32 10 174 = 0% 337 1 ² = 0%	0.0% 0.6% 0.0% 5.2% 100.0% %	-14.90 [+16.18, -13.62] -680 [1542, 182 -69.20 [+96.54, -41.86 22.00 [10.83, 33.17 -4.45 [-7.45, -1.45 -5.53 [-6.21, -4.84	21 21 21 41 -100 -50 -50 -50 -50 -50 -50 -50 -
amour2016 am2haili2017 corletti2020 havakhi2013 forg2013 ubtotal (95% CL) elerogeneity: Tau ² = est for overail effect: otal (95% CL) elerogeneity: Tau ² = est for overail effect: est for subaroup diff tudy or Subgroup 5.1.1 GGT <12	24.3 32.7 34 44.2 37 = 0.00; Ch : Z = 2.91 = 0.00; Ch : Z = 15.8; fferences: Exp Mean	7.7 2.4 16.8 33.9 6 $hi^2 = 4.37$ (P = 0.0 $hi^2 = 10.3$ 3 (P < 0.2) $: Chi^2 = 0$ periment SD	32 38 45 31 10 170 7, df = 104) 341 39, df .0000 0.52. c 	47.6 40.8 113.4 15 5 (P = 0. = 12 (P = 1) if = 1 (P =	3.2 24 71 17 50); I ² : 0.58); = 0.47) Contr n <u>S</u>	37 44 32 10 174 = 0% 337 I ² = 0% . I ² = 0 01 50 To	0.0% 0.6% 0.0% 5.2% 100.0% %	-14.90 [+16.18, -13.62] -6.80 [15.42, 1.83 -69.20 [+96.54, -41.86 22.00 [10.83, 33.17 -4.45 [-7.45, -1.45 -5.53 [-6.21, -4.84 Mean Different ight IV, Random, 95	21 21 21 21 21 21 21 21 21 21
amour2016 iam2haili2017 contetti2020 havashi/2013 ofong2013 ubtotal (95% CI) eterogeneity: Tau ² = est for overail effect otal (95% CI) eterogeneity: Tau ² = est for overail effect est for overail effect est for subaroup diff tudy or Subgroup 5.1.1 GGT <12 avadi2017	24.3 32.7 34 44.2 37 = 0.00; Ch : Z = 2.91 = 0.00; Ch : Z = 15.8; fferences: Exp Mean 35.75	7.7 2.4 16.8 33.9 6 $hi^{\mu} = 4.37$ (P = 0.0 $hi^{\mu} = 10.3$ 3 (P < 0.0 $: Chi^{\mu} = 0$ berimen 5D 16.35	32 38 45 31 10 170 7, df = 104) 341 39, df .0000 0.52. c attal Tota 170 170 170 170 170 170 170 170	47.6 40.8 113.4 15 5 (P = 0. = 12 (P = 1) if = 1 (P = al Mean 9 35.8:	3.2 24 71 17 50); I ² = 0.58); = 0.47) Contr n <u>\$</u> 9 21.3	37 44 32 10 174 = 0% 337 ² = 0% . ² = 0 0 50 To	0.0% 0.6% 0.0% 5.2% 100.0% % %	-14.90 [+16.18, -13.62] -6.80 [15.42, 1.83 -69.20 [96.54, -41.88 22.00 [10.83, 33.17 -4.45 [-7.45, -1.45 -5.53 [-6.21, -4.84 Mean Different ight	21 21 21 21 21 21 21 21 21 21
amour2016 lanzhaili2017 corlett/2020 harakhi2013 iong2013 ubtotal (95% CL) letterogeneik/Tau*= est for overail effect otal (95% CL) letterogeneik/Tau*= est for overail effect est for subarouo diff	24.3 32.7 34 44.2 37 = 0.00; Ch : Z = 2.91 = 0.00; Ch : Z = 15.8 fferences: Exp Mean 35.75 41.13	7.7 2.4 16.8 33.9 6 $hi^2 = 4.37$ (P = 0.0 $hi^2 = 10.3$ 3 (P < 0. Chi ² = 0 Chi ² = 0 SD 5 16.35 5.3	32 38 45 31 10 170 7, df = 1004) 341 39, df = 1004) 341 39, df = 10052, df = 10052	47.6 40.8 113.4 15 5 (P = 0. = 12 (P = 1) if = 1 (P = al Mean 9 35.8 0 46.2	3.2 24 71 17 50); P : 0.58); = 0.47) Contr n S 9 21.1 6 4.4	37 44 32 10 174 = 0% 337 ² = 0% . ² = 0 0 6 <u>D</u> To 77 44	0.0% 0.6% 0.0% 5.2% 100.0% % % tal We 20 0 28 17	-14.90 [+16.18, -13.62] -6.80 [+5.42, 1.83 -69.20 [+96.54, -41.86 22.00 [10.83, 33.17 -4.45 [-7.45, -1.45 -5.53 [-6.21, -4.84 Mean Different IV, Random, 95 .8% -0.14 [+12.18, 17 -4% -5.13 [-7.64, -2]	21 21 21 21 21 21 21 21 21 21
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amour2016 ambalil2017 corleti/2020 havakhi2013 ong2013 ubtotal (95% CI) eterogeneiky: Tau ² = est for overall effect tatal (95% CI) eterogeneiky: Tau ² = est for overall effect est for subaroup diff tudy or Subgroup 5.1.1 GGT <12 vadi2017 obyliak2018 obyliak 2018 obyliak 2019	24.3 32.7 34 44.2 37 = 0.00; Ch : Z = 2.91 = 0.00; Ch : Z = 15.8 fferences: Exp Mean 35.75 41.13	7.7 2.4 16.8 33.9 6 $hi^{\mu} = 4.37$ (P = 0.0 $hi^{\mu} = 10.3$ 3 (P < 0.) $: Chi^{\mu} = 0$ berimen SD 16.35 5.3 6.32	32 38 45 31 10 170 7, df = 1004) 341 339, df .00000 0.52, c .0000	47.6 40.8 113.4 15 5 (P = 0. = 12 (P = 1) if = 1 (P = al Mean 9 35.8 0 46.2	3.2 24 71 17 50); I ² : 0.58); = 0.47) Contr n <u>S</u> 9 21.1 6 4.4 3 4	37 44 32 10 174 = 0% 337 ² = 0% 0 5 <u>D</u> To 77 44	0.0% 0.6% 0.0% 5.2% 100.0% % % tal We 20 0 28 17 22 11 24	-14.90 [+16.18, -13.62] -6.80 [+5.42, 1.83 -69.20 [+96.54, -41.86 22.00 [10.83, 33.17 -4.45 [-7.45, -1.45 -5.53 [-6.21, -4.84 Mean Different IV, Random, 95 .8% -0.14 [+12.18, 17 -4% -5.13 [-7.64, -2]	21 21 21 21 21 21 21 21 21 21
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amouri2016 lanzhaili2017 corlett/2020 havakhi2013 forg2013 ubtotal (95% CL) letterogeneity: Tau ² = est for overail effect detrogeneity: Tau ² est for overail effect est for subarouo diff <u>tudy or Subarouo</u> diff <u>5.1.1 GGT <12</u> avadi2017 obyliak2018 obyliak2018 obyliak2019 ubtotal (95% CL) letterogeneity: Tau ² est for overail effect 5.1.2 GGT >12	24.3 32.7 34 44.2 37 = 0.00; Ch : Z = 2.91 = 0.00; Ch : Z = 15.8; fferences: Exp Mean 35.75 41.13 41.78 41.65 2 = 0.42; C : t: Z = 5.49	$\begin{array}{c} 7.7\\ 2.4\\ 16.8\\ 33.9\\ 6\\ 11^{2}=4.37\\ (P=0.0\\ 10^{2}=10.3\\ 3(P<0.0\\ 10^{2}=10.3\\ (P=0.0\\ 10^{2}=10.3\\ $	32 38 45 31 10 170 7, df = 1004) 341 39, df = 0.0000 0.52, c 1 32, df = 22, df 0.0000 7, 22, df	47.6 40.8 113.4 15 5 (P = 0. = 12 (P = 0. = 12 (P = 0. = 11 Mean 9 35.8 0 46.2 6 49.2 5 = 2 (P = 1.)	3.2 24 71 17 50); P : 0.58); : 0.58)	37 44 32 174 = 0% 337 P = 0% 50 50 50 77 44 89 4 P = 1(0.0% 0.6% 0.0% 5.2% 100.0% % * * * * * * * * * * * * * * * * * *	-14.90 [+16.18, -13.62 -6.80 [15.42, 183 -6.920 [-96.54, -41.86 2.200 [10.83, 33.17] -4.45 [-7.45, -1.45 -5.53 [-6.21, -4.84 Mean Different ight <u>V, Random, 95</u> 8% -0.14 [-12.18, 17 -% -5.13 [-7.54, -7 Not estim .9% -5.92 [-8.03, -2	21 21 21 21 21 21 21 21 21 21
amour2016 lambail/2017 contetti/2020 havakhi/2013 (orog/2013 ubtotal (95% CL) leterogeneity: Tau ² = est for overail effect: otal (95% CL) leterogeneity: Tau ² = est for overail effect: est for subaroup diff st.1.1 GGT <12 avadi/2017 cobyliak/2018 (obyliak/2018 dobyliak/2018 dobyliak/2019 ubtotal (95% CL) leterogeneity: Tau ² est for overail effect 5.1.2 GGT >12 letr2011	24.3 32.7 34 44.2 37 = 0.00; Ch : Z = 2.91 = 0.00; Ch : Z = 15.8; fferences: Exp Mean 35.75 41.13 41.78 41.85 2 = 0.42; C : Z = 5.44 107.7	$\begin{array}{c} 7.7\\ 2.4\\ 16.8\\ 33.9\\ 6\\ 1^{12}=4.37\\ 0\\ 1^{12}=10.3\\ 0\\ 0\\ 1^{12}=10.3\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\$	32 38 45 31 10 170 7, df = 0000 0.52, c 139, df 0000 0.52, c 139, df 22, df 0.0000 122, df 122, df 100 100 100 100 100 100 100 10	47.6 40.8 113.4 15 5 (P = 0 = 12 (P = 1) if = 1 (P	3.2 24 71 17 50); P : 0.58); = 0.47) Contr n \$ 9 21.: 6 4.4 3 4 1 1.5 0.33); 6 6 65	37 44 32 174 = 0% 337 * = 0% 0 5 5 5 77 44 8 8 4 1 [°] = 10 5 77	0.0% 0.6% 0.0% 5.2% 100.0% % * * * * * * * * * * * * * * * * * *	-14.90.[+16.18, -13.62 -6.80.[+5.42, 1.83 -6.80.[+5.42, 1.83 -6.92.00.[+0.63, -3.18 -22.00.[10.83, 33.17 -4.45.[-7.45, -1.45 -5.53.[-6.21, -4.84 Mean Different istht <u>IV. Random, 95</u> 8.% -0.14.[+12.18, 1] -5.53.[-7.64, -7 Not estim 9.% -5.92.[-8.03, -2 .1% 24.10.[-22.64, 7]	21 21 21 41 -100 -50 0 50 100 Favours [experimental] Favours [control] Ce Mean Difference 5% CI V. Random, 95% CI 1.90] 2.62] 4.39] 1able 3.81] 4 0.84]
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Figure 12. different in Liver function levels. The results of the analysis showed that after excluding studies with heterogeneity sources, the improvement of ALT, GGT, TG, blood glucose and other outcomes in studies with a course of treatment greater than or equal to 12 weeks was significantly better than that of studies

GGT, TG, blood glucose and other outcomes in studies with a course of treatment greater than or equal to 12 weeks was significantly better than that of studies with a treatment course of less than 12 weeks; while AST, TC, and BMI On the contrary. ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GGT = glutamyl transpeptidase, TC = total cholesterol, TG = triglyceride.

Formal analysis: Xiangyu Zhou, Jincheng Wang, Leiming Mao. Investigation: Xiangyu Zhou, Zuoyu Ye. Methodology: Xiangyu Zhou, Jiajia Liao. Resources: Xiangyu Zhou. Software: Xiangyu Zhou. Supervision: Sufang Zhou. Writing – original draft: Xiangyu Zhou. Writing – review & editing: Sufang Zhou.

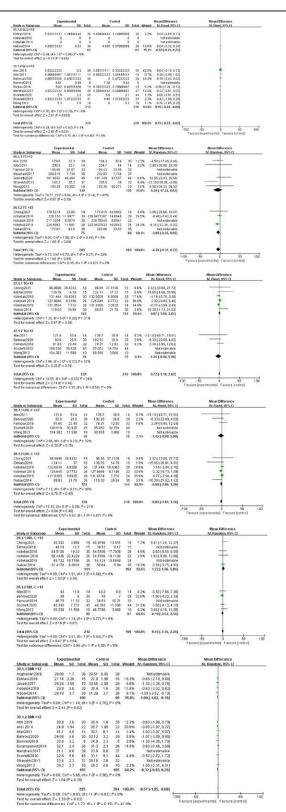


Figure 13. Different in lipid levels. Probiotics were more effective in treating BMI and HDL-C when the treatment duration was less than 12 weeks. BMI = body mass index.

References

- Maurice J, Manousou P. Non-alcoholic fatty liver disease. Clin Med (Lond). 2018;18:245–50.
- [2] Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15:11–20.

- [3] Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;346:1221–31.
- [4] Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67:328–57.
- [5] Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology. 2010;52:1836–46.
- [6] Ko E, Yoon EL, Jun DW. Risk factors in nonalcoholic fatty liver disease. Clin Mol Hepatol. 2022.
- [7] Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell. 2006;124:837–48.
- [8] Bäckhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci USA. 2004;101:15718–23.
- [9] Abenavoli L, Maurizi V, Rinninella E, et al. Fecal microbiota transplantation in NAFLD treatment. Medicina (Kaunas). 2022;58:1559.
- [10] Takaki A, Kawai D, Yamamoto K. Multiple hits, including oxidative stress, as pathogenesis and treatment target in non-alcoholic steatohepatitis (NASH). Int J Mol Sci. 2013;14:20704–28.
- [11] Kim JJ, Sears DD. TLR4 and insulin resistance. Gastroenterol Res Pract. 2010;2010:212563.
- [12] Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56:1761–72.
- [13] Crispe IN. Liver antigen-presenting cells. J Hepatol. 2011;54:357-65.
- [14] Beutler B, Hoebe K, Du X, et al. How we detect microbes and respond to them: the Toll-like receptors and their transducers. J Leukoc Biol. 2003;74:479–85.
- [15] 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. Obes Facts. 2016;9:65–90.
- [16] Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. NASH Clinical Research Network. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet. 2015;385:956–65.
- [17] Rotman Y, Sanyal AJ. Current and upcoming pharmacotherapy for non-alcoholic fatty liver disease. Gut. 2017;66:180–90.
- [18] Slavin J. Fiber and prebiotics: mechanisms and health benefits. Nutrients. 2013;5:1417–35.
- [19] Dewulf EM, Cani PD, Claus SP, et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. Gut. 2013;62:1112–21.
- [20] Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2019.
- [21] Ahn SB, Jun DW, Kang BK, et al. Randomized, double-blind, placebo-controlled study of a multispecies probiotic mixture in nonalcoholic fatty liver disease. Sci Rep. 2019;9:5688.
- [22] Alisi A, Bedogni G, Baviera G, et al. Randomised clinical trial: the beneficial effects of VSL#3 in obese children with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2014;39:1276–85.
- [23] Aller R, De Luis DA, Izaola O, et al. Effect of a probiotic on liver aminotransferases in nonalcoholic fatty liver disease patients: a double blind randomized clinical trial. Eur Rev Med Pharmacol Sci. 2011;15:1090–5.
- [24] Asgharian A, Askari G, Esmailzade A, et al. The effect of symbiotic supplementation on liver enzymes, c-reactive protein and ultrasound findings in patients with non-alcoholic fatty liver disease: a clinical trial. Int J Prev Med. 2016;7:59.
- [25] Behrouz V, Aryaeian N, Zahedi MJ, et al. Effects of probiotic and prebiotic supplementation on metabolic parameters, liver aminotransferases, and systemic inflammation in nonalcoholic fatty liver disease: a randomized clinical trial. J Food Sci. 2020;85:3611–7.
- [26] Bomhof MR, Parnell JA, Ramay HR, et al. Histological improvement of non-alcoholic steatohepatitis with a prebiotic: a pilot clinical trial. Eur J Nutr. 2019;58:1735–45.
- [27] Chong PL, Laight D, Aspinall RJ, et al. A randomised placebo controlled trial of VSL#3[®] probiotic on biomarkers of cardiovascular risk and liver injury in non-alcoholic fatty liver disease. BMC Gastroenterol. 2021;21:144.
- [28] Duseja A, Acharya SK, Mehta M, et al. High potency multistrain probiotic improves liver histology in non-alcoholic fatty liver disease (NAFLD): a randomised, double-blind, proof of concept study. BMJ Open Gastroenterol. 2019;6:e000315.

- [29] Ekhlasi G, Kolahdouz Mohammadi R, Agah S, et al. Do symbiotic and Vitamin E supplementation have favorite effects in nonalcoholic fatty liver disease? A randomized, double-blind, placebo-controlled trial. J Res Med Sci. 2016;21:106.
- [30] Eslamparast T, Poustchi H, Zamani F, et al. Synbiotic supplementation in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. Am J Clin Nutr. 2014;99:535–42.
- [31] Famouri F, Shariat Z, Hashemipour M, et al. Effects of probiotics on nonalcoholic fatty liver disease in obese children and adolescents. J Pediatr Gastroenterol Nutr. 2017;64:413–7.
- [32] Javadi L, Ghavami M, Khoshbaten M, et al. The effect of probiotic and/or prebiotic on liver function tests in patients with nonalcoholic fatty liver disease: a double blind randomized clinical trial. Iranian Red Crescent Med J. 2017. In press.
- [33] Kobyliak N, Abenavoli L, Mykhalchyshyn G, et al. A multi-strain probiotic reduces the fatty liver index, cytokines and aminotransferase levels in NAFLD patients: evidence from a randomized clinical trial. J Gastrointestin Liver Dis. 2018;27:41–9.
- [34] Kobyliak N, Abenavoli L, Falalyeyeva T, et al. Beneficial effects of probiotic combination with omega-3 fatty acids in NAFLD: a randomized clinical study. Minerva Med. 2018;109:418–28.
- [35] Kobyliak N, Abenavoli L, Mykhalchyshyn G, et al. Probiotics and smectite absorbent gel formulation reduce liver stiffness, transaminase and cytokine levels in NAFLD associated with type 2 diabetes: a randomized clinical study. Clin Diabetol. 2019;8:205–14.
- [36] Manzhalii E, Virchenko O, Falalyeyeva T, et al. Treatment efficacy of a probiotic preparation for non-alcoholic steatohepatitis: a pilot trial. J Dig Dis. 2017;18:698–703.
- [37] Nabavi S, Rafraf M, Somi MH, et al. Effects of probiotic yogurt consumption on metabolic factors in individuals with nonalcoholic fatty liver disease. J Dairy Sci. 2014;97:7386–93.
- [38] Scorletti E, Afolabi PR, Miles EA, et al. Synbiotics alter fecal microbiomes, but not liver fat or fibrosis, in a randomized trial of patients with nonalcoholic fatty liver disease. Gastroenterology. 2020;158:1597– 610.e7.
- [39] Shavakhi A, Minakari M, Firouzian H, et al. Effect of a probiotic and metformin on liver aminotransferases in non-alcoholic steatohepatitis: a double blind randomized clinical trial. Int J Prev Med. 2013;4:531–7.
- [40] Vajro P, Mandato C, Licenziati MR, et al. Effects of Lactobacillus rhamnosus strain GG in pediatric obesity-related liver disease. J Pediatr Gastroenterol Nutr. 2011;52:740–3.

- [41] Wong VW, Won GL, Chim AM, et al. Treatment of nonalcoholic steatohepatitis with probiotics. A proof-of-concept study. Ann Hepatol. 2013;12:256–62.
- [42] Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease – meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64:73–84.
- [43] Marra F, Svegliati-Baroni G. Lipotoxicity and the gut-liver axis in NASH pathogenesis. J Hepatol. 2017;68:280–95.
- [44] Vatner DF, Majumdar SK, Kumashiro N, et al. Insulin-independent regulation of hepatic triglyceride synthesis by fatty acids. Proc Natl Acad Sci USA. 2015;112:1143–8.
- [45] Dai X, Hou H, Zhang W, et al. Microbial metabolites: critical regulators in NAFLD. Front Microbiol. 2020;11:567654.
- [46] Tang Y, Huang J, Zhang WY, et al. Effects of probiotics on nonalcoholic fatty liver disease: a systematic review and meta-analysis. Therap Adv Gastroenterol. 2019;12.
- [47] Sharpton SR, Maraj B, Harding-Theobald E, et al. Gut microbiometargeted therapies in nonalcoholic fatty liver disease:a systematic review, meta-analysis, and meta-regressionx. Am J Clin Nutr. 2019;110:139–49.
- [48] Khan MY, Mihali AB, Rawala MS, et al. The promising role of probiotic and synbiotic therapy in aminotransferase levels and inflammatory markers in patients with nonalcoholic fatty liver disease – a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2019;31:1.
- [49] Loman BR, Hernández-Saavedra D, An R, et al. Prebiotic and probiotic treatment of nonalcoholic fatty liver disease: a systematic review and meta-analysis. Nutr Rev. 2018;76:822–39.
- [50] Haro C, Garcia-Carpintero S, Alcala-Diaz JF, et al. The gut microbial community in metabolic syndrome patients is modified by diet. J Nutr Biochem. 2016;27:27–31.
- [51] Mitsou EK, Kakali A, Antonopoulou S, et al. Adherence to the Mediterranean diet is associated with the gut microbiota pattern and gastrointestinal characteristics in an adult population. Br J Nutr. 2017;117:1645–55.
- [52] Castro-Acosta ML, Sanders TAB, Reidlinger DP, et al. Adherence to UK dietary guidelines is associated with higher dietary intake of total and specific polyphenols compared with a traditional UK diet: further analysis of data from the Cardiovascular risk REduction Study: supported by an Integrated Dietary Approach (CRESSIDA) randomised controlled trial. Br J Nutr. 2019;121:402–15.
- [53] Malesza IJ, Malesza M, Walkowiak J, et al. High-fat, western-style diet, systemic inflammation, and Gut microbiota: a narrative review. Cells. 2021;10:3164.