Systematic Review and Meta-Analysis

Medicine

OPEN

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.

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

This research was funded by the following funding projects: National Natural Science Foundation of China (81460683); Science and Technology Project Plan of Guizhou Province (Supported by Qian Kehe [2021] General 015).

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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How to cite this article: Zhou X, Wang J, Zhou S, Liao J, Ye Z, Mao L. Efficacy of probiotics on nonalcoholic fatty liver disease: A meta-analysis. Medicine 2023;102:4(e32734).

Received: 5 August 2022 / Received in final form: 3 January 2023 / Accepted: 4 January 2023

http://dx.doi.org/10.1097/MD.0000000000032734

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-Kβ 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 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 systematically 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 nonalcoholic liver efficacy and safety.

Table 1

Basic characteristics 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 mixture	Placebo	12	1.2.4.5.6.7.8.9.10.11.12.13.15.16	MRI
Alisi[22]	2014	11 ± 2/10 ± 2	Spain	22/22	VSL#3	Placebo	16	1.5.10.15.17	Hepatic biopsy
Aller[23]	2011	44.3 ± 15.1/49.4 ± 10.9	Iran	14/14	Lactobacillus bulgaricus and streptococcus thermophilus	Placebo	12	1.2.3.4.6.7.8.9.10.11.12.15.16	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 ± 10.09/38.46 ± 7.11	Canada	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 ± 7/57 ± 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 preparation	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 supplementation	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 ± 9.11/43.90 ± 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	Probiotic-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 ± 1.3/44.3 ± 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 ± 13.1/50.2 ± 12.4	Denmark	44/45	Prebiotic	Placebo	40–56	1.2.3.4.5.6.7.8.9.13.15	MRS
Shavakhi[39]	2013	46.9 ± 5.2/46.9 ± 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 ± 9/55 ± 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	N0	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	N0	N0	Y1	3	Lower

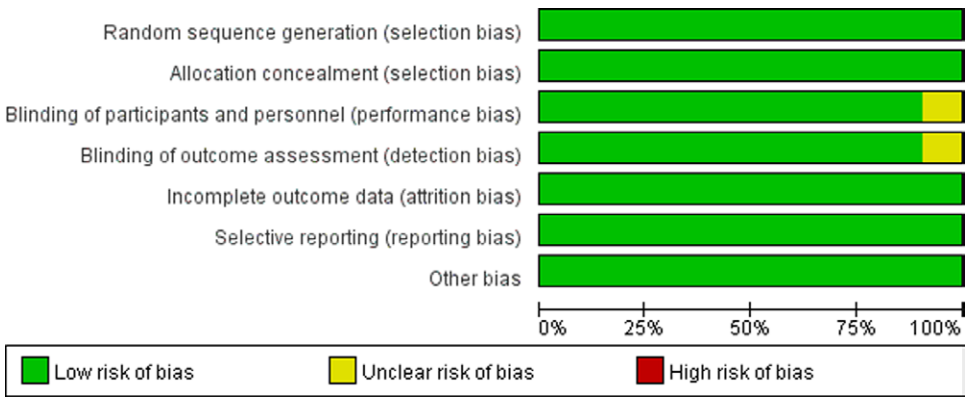

Figure 1. Risk of bias graph. A total of 21 studies that met the criteria were finally included in the meta-analysis. Three of the study participants were children, and one of the study participants had coexisting type 2 diabetes; two of the studies were not explicitly blinded, and one study was not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

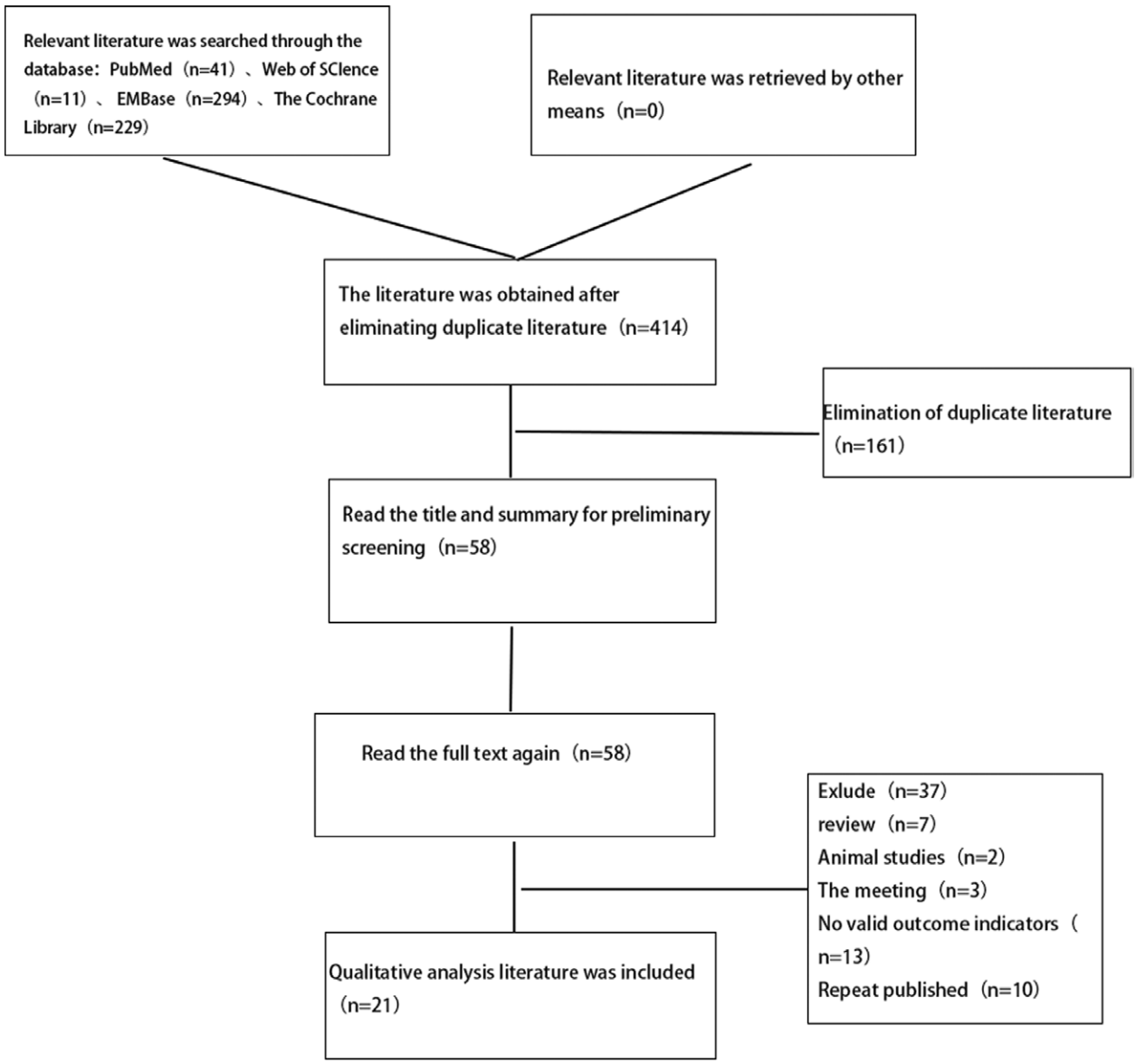

Figure 3. Flowchart of study selection. The process of literature search, evaluation, exclusion, and inclusion is shown in Figure 3. A total of 21 research reports were finally included, involving 1037 participants.

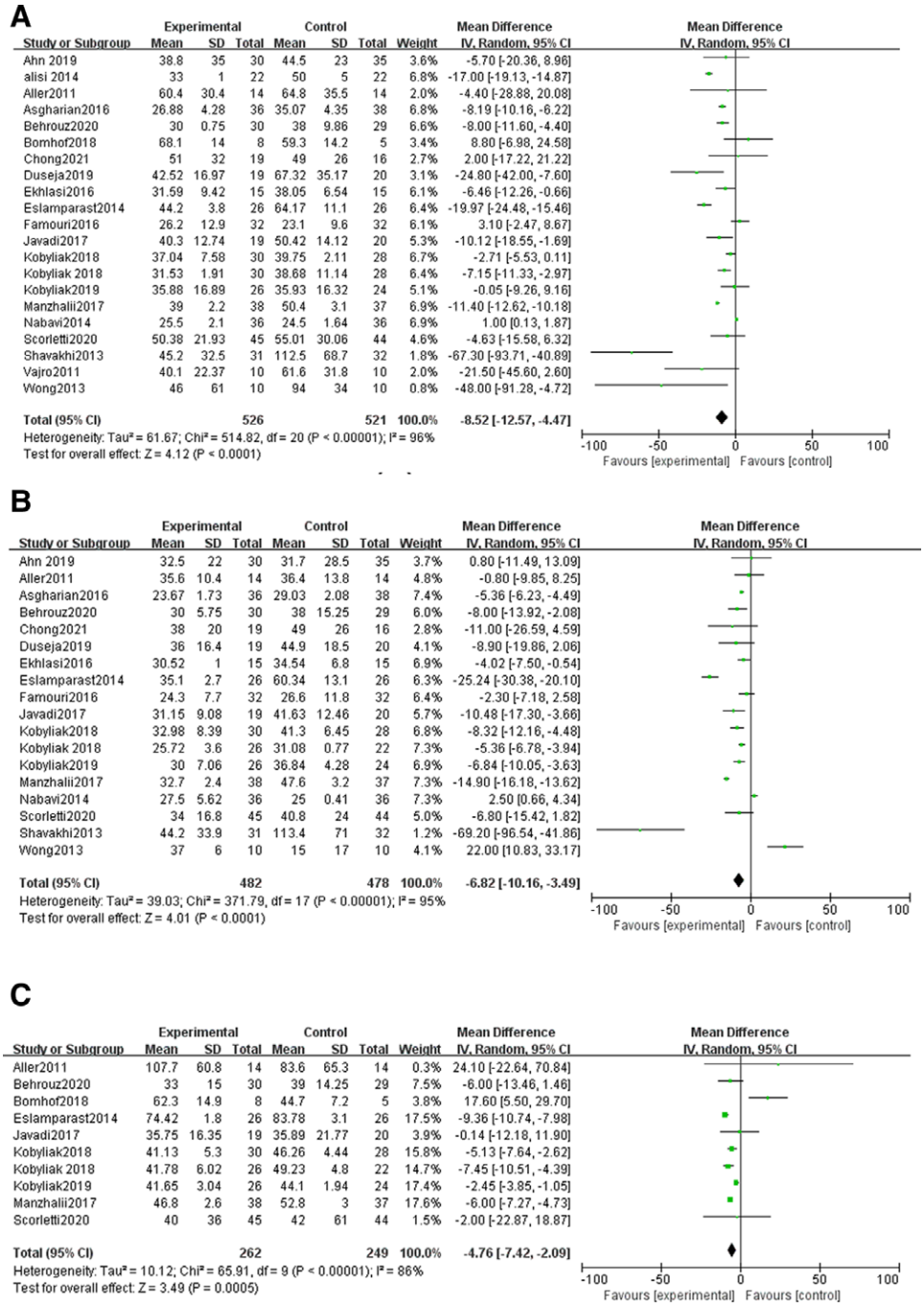

Figure 4. The Liver Function Levels. A total of 21 studies reported the mean change in ALT from baseline (A): the results of the analysis showed that ALT levels were significantly reduced after probiotic intervention, A total of 18 studies reported the mean change from baseline in AST (B): the analysis 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).

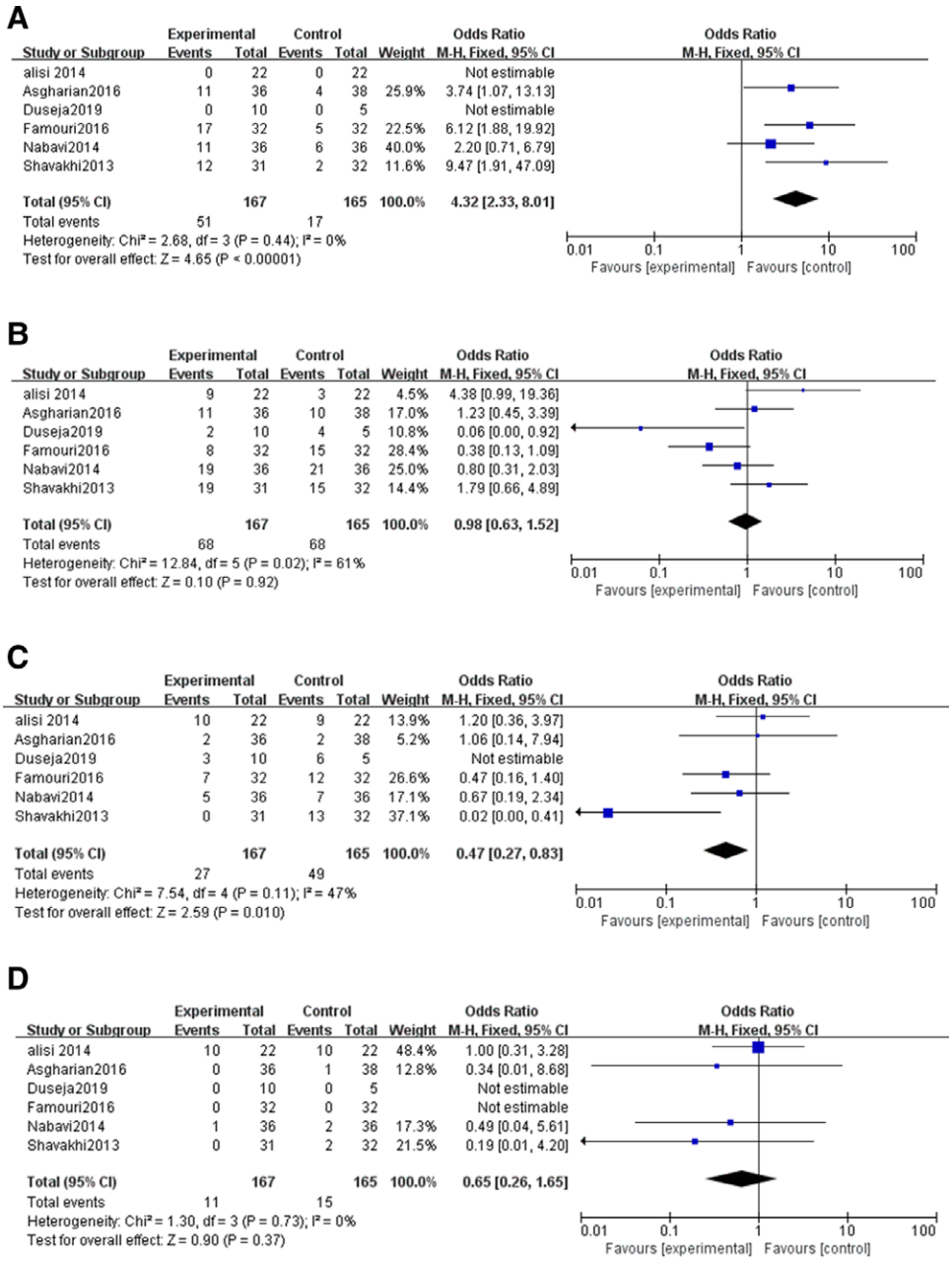

Figure 5. The Hepatocyte Steatosis. the results of the analysis showed that the degree of hepatic steatosis was significantly improved after the intervention with probiotic therapy, with steatosis grade 0. the results showed that only steatosis grades 0 and 2 were statistically significant.

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

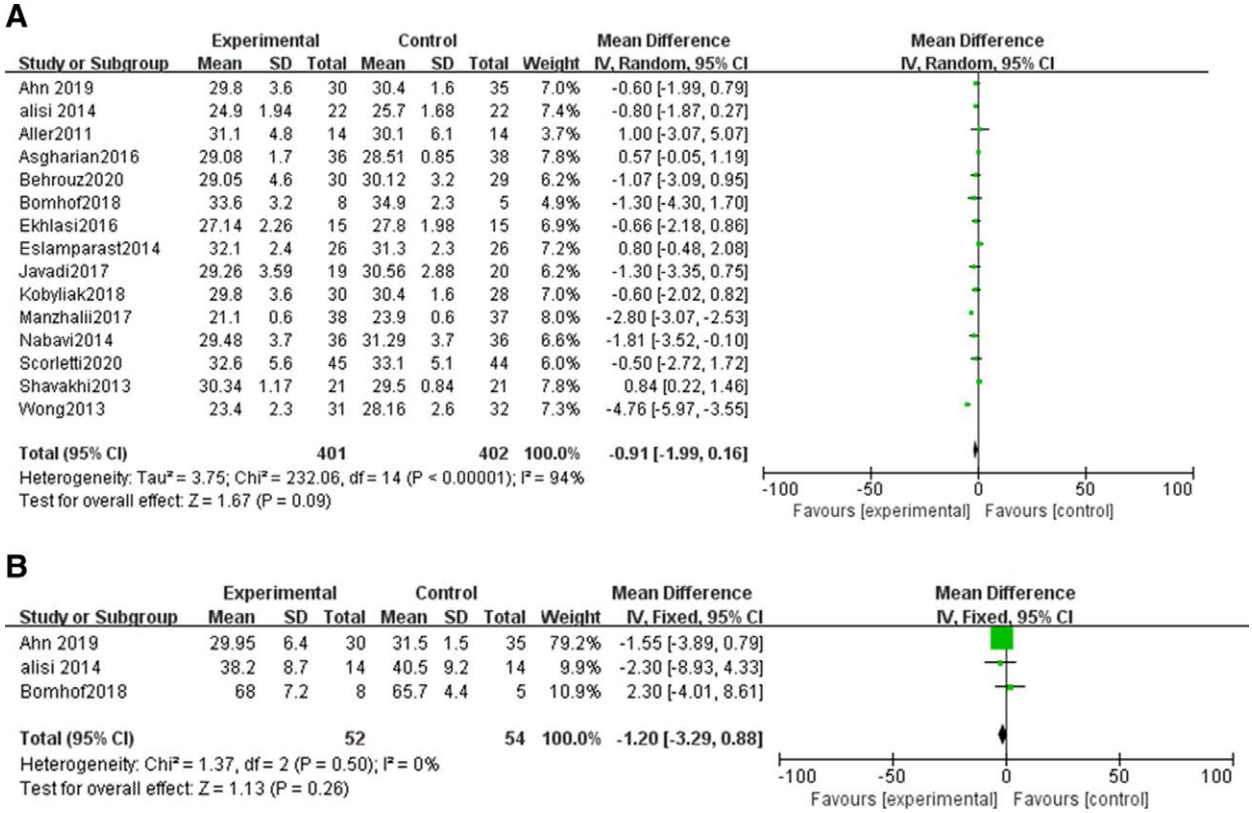

Figure 6. The total fat mass levels and BMI. A total of 3 studies reported changes from baseline in total fat mass levels (A): the results of the analysis showed that after probiotic intervention, total fat content was reduced; A total of 15 studies reported changes in BMI from baseline (B): the analysis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

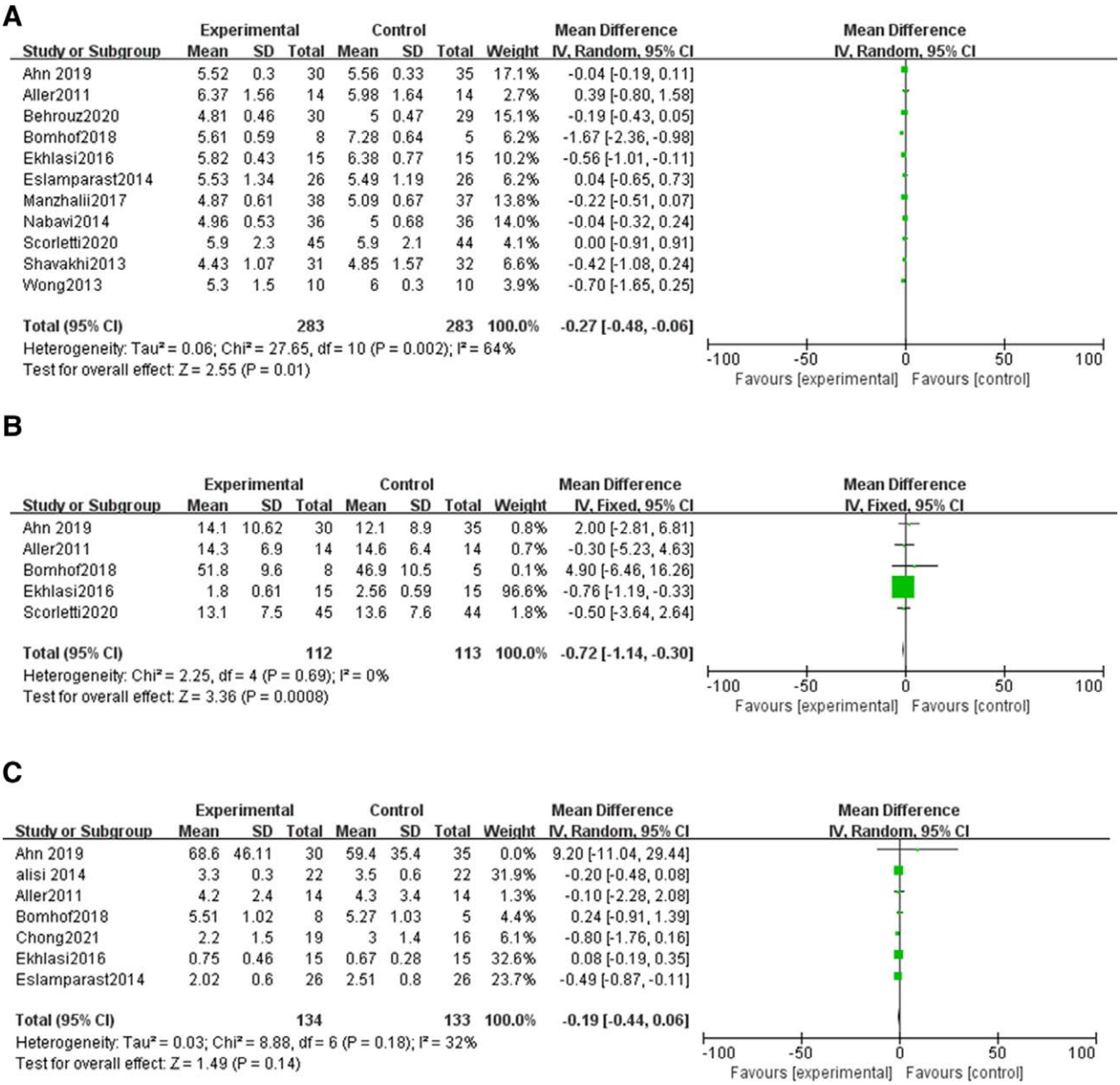

Figure 7. The blood glucose and insulin levels. A total of 11 studies reported changes in blood glucose from baseline (A): the analysis showed that blood glucose levels decreased after probiotic intervention. A total of 5 studies reported changes in insulin from baseline (B): the analysis showed that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

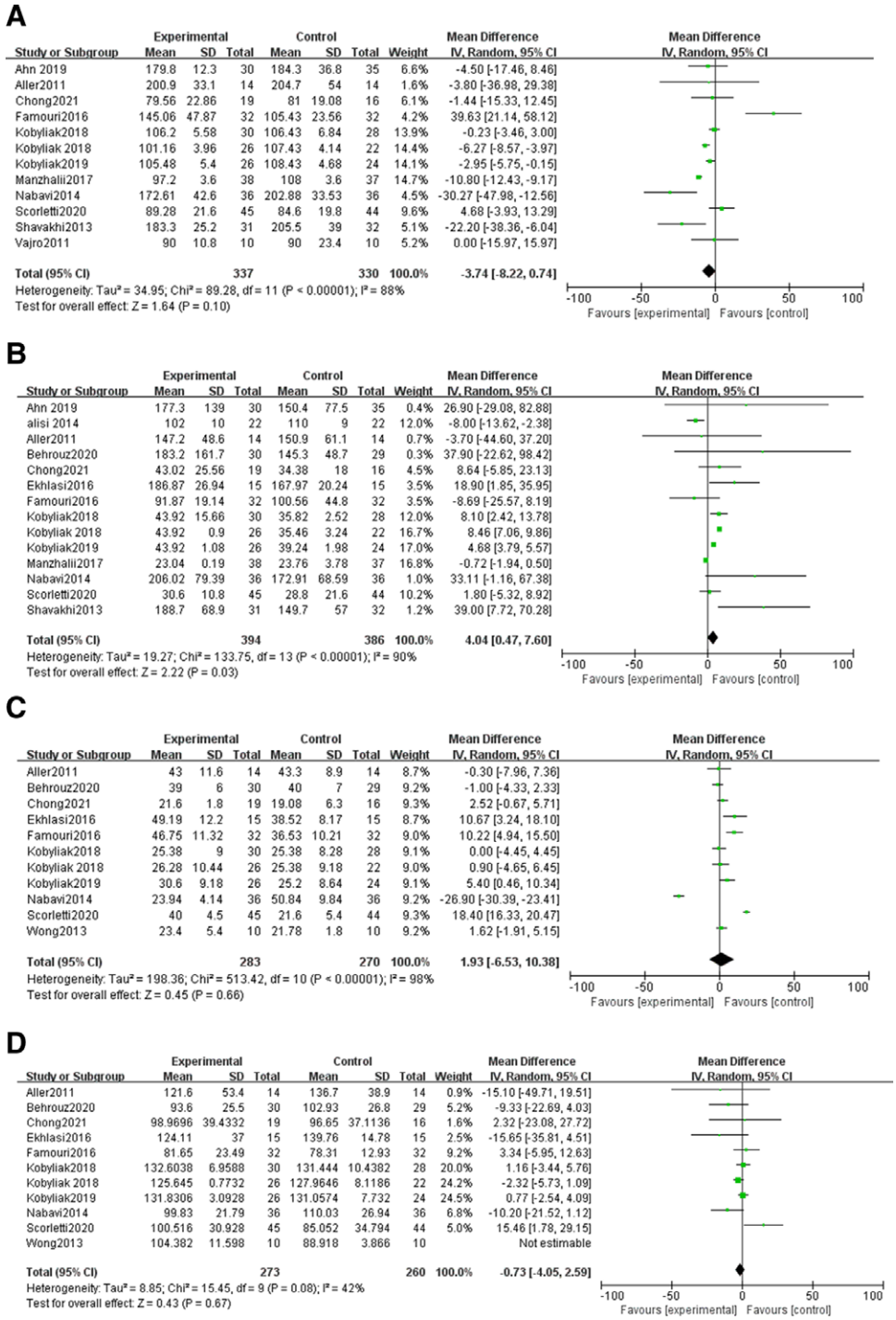

Figure 8. The blood lipid levels. A total of 12 studies reported changes in TC levels from baseline (A): the analysis showed that TC levels were significantly reduced after probiotic intervention. A total of 15 studies reported changes in TG compared to pre-baseline (B): the analysis showed that TG levels 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

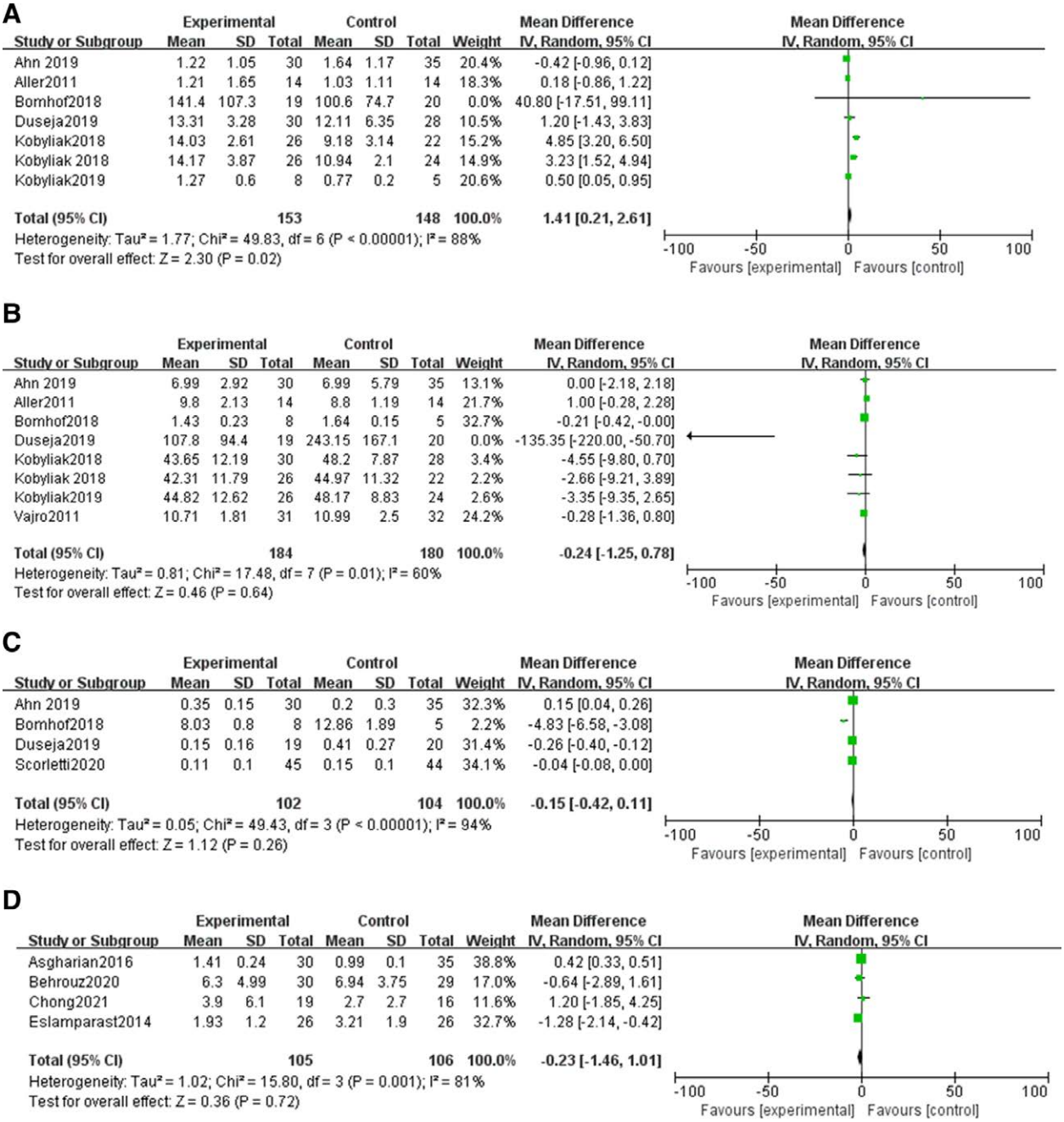

Figure 9. The inflammatory factors levels. A total of 7 studies reported changes in IL-6 from baseline (A): the analysis showed that IL-6 was elevated after probiotic intervention. A total of 8 studies reported changes in TNF-α from baseline (B): the analysis showed that after probiotic intervention, 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

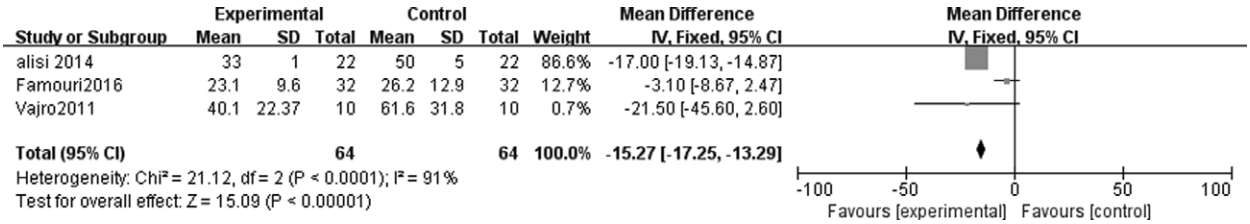

Figure 10. The ALT levels in children. A total of 3 studies reported the efficacy of probiotics in the treatment of children with NAFLD, but only ALT levels met the criteria for meta-analysis. The analysis results showed that after probiotic intervention, the ALT level in the children group was significantly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

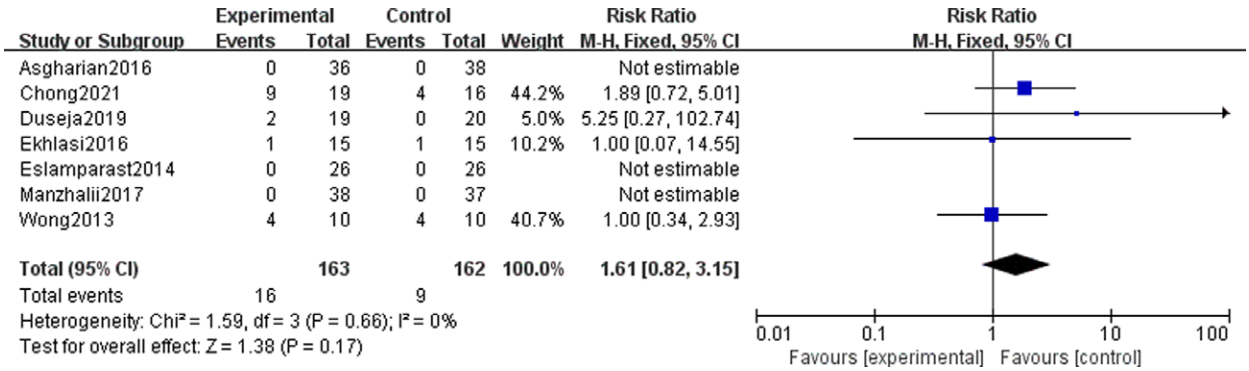

Figure 11. The Adverse Reactions. A total of 7 studies explicitly reported adverse reactions: the analysis showed that the incidence of adverse reactions was higher in the probiotic therapy group than in the placebo group.

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.

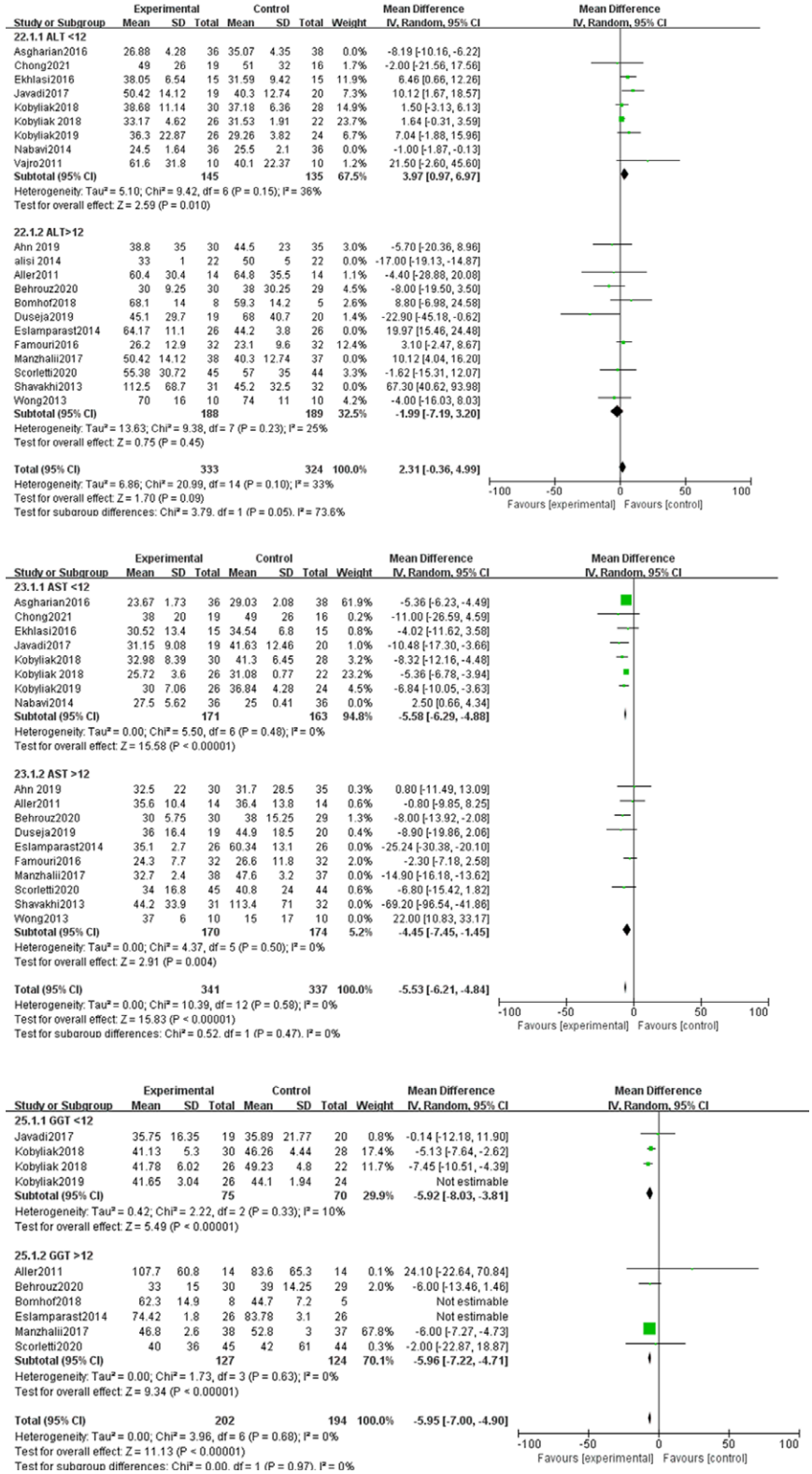

Figure 12. different in Liver function levels. The results of the analysis showed that after excluding studies with heterogeneity sources, the improvement of ALT, GGT, TG, blood glucose and other outcomes in studies with a course of treatment greater than or equal to 12 weeks was significantly better than that of studies 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.

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Supervision: Sufang Zhou.
Writing – original draft: Xiangyu Zhou.
Writing – review & editing: Sufang Zhou.

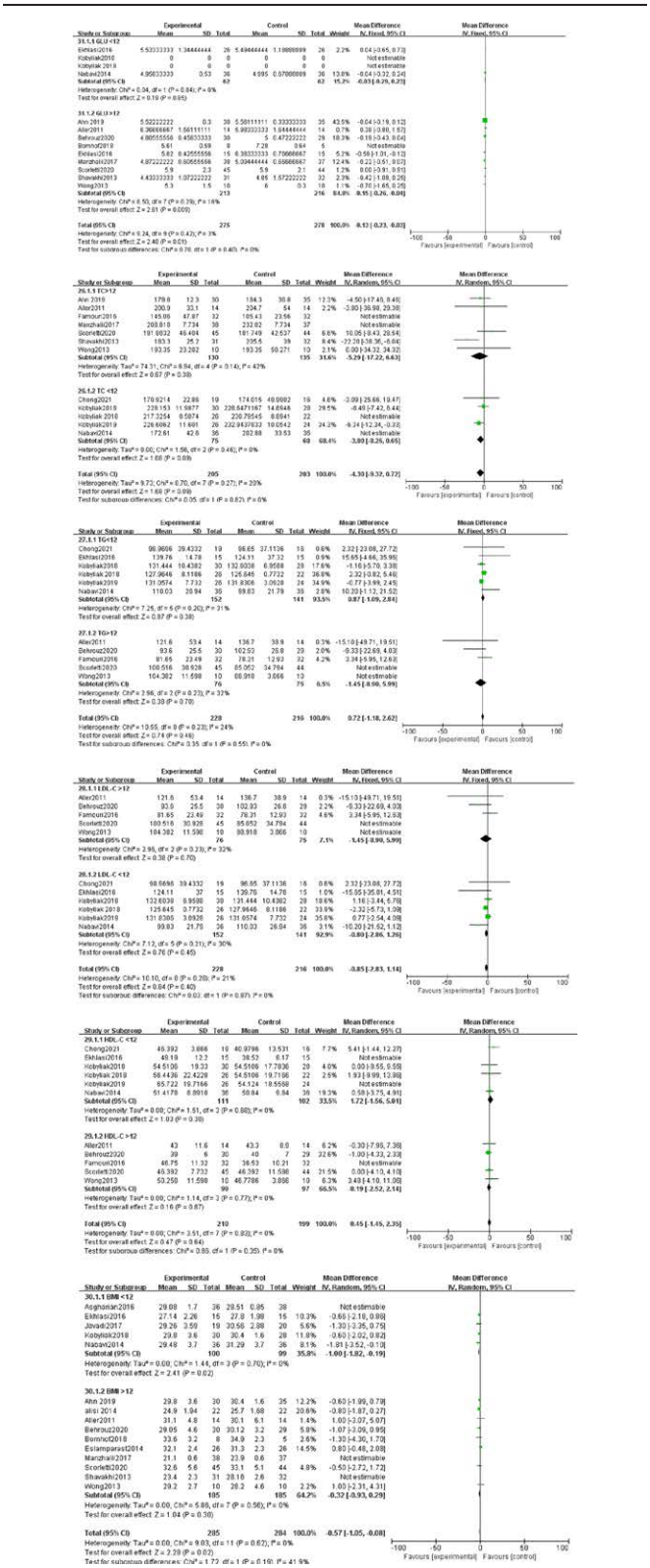

Figure 13. Different in lipid levels. Probiotics were more effective in treating BMI and HDL-C when the treatment duration was less than 12 weeks. BMI = body mass index.

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