Systematic Review and Meta-Analysis

Medicine

OPEN

Statins on nonalcoholic fatty liver disease
A systematic review and meta-analysis of 14 RCTs

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Abstract

Background: The prevalence of nonalcoholic fatty liver disease (NAFLD) is rising rapidly in the world. Our aim is to investigate the efficacy and safety of statins in the treatment of NAFLD.

Methods: This study was conducted by searching The National Library of Medicine, Cochrane Library, China National Knowledge Infrastructure, Web of Science, and Wanfang Data Knowledge Service Platform databases. Literature data are expressed as mean difference (MD) and 95% confidence intervals (CIs) or relative risk and 95% CI. For $I^2 > 50\%$ trials, random effect model is used for statistical analysis, otherwise fixed effect model is used.

Results: Fourteen studies are selected for this meta-analysis, which includes totally 534 patients in the treatment group and 527 patients in the control group. As a result, 5 studies show that the total effective rate of the treatment group is 17% higher than that of the control group ($Z = 2.11$, relative risk = 1.17, 95% CI: [1.01–1.35]). Twelve studies show that alanine aminotransferase levels of the experimental group are lower than that of the control group ($Z = 2.63$, $P = .009$, MD = –5.53, 95% CI: [–9.64 to –1.41]). Eleven studies show that aspartate transaminase levels of the experimental group are lower than that of the control group ($Z = 2.01$, $P = .04$, MD = –3.43, 95% CI: [–6.77 to –0.08]). Six studies show that alkaline phosphatase levels of the experimental group are lower than that of the control group ($Z = 0.79$, $P = .43$, MD = –3.46, 95% CI: [–12.08 to 5.16]). Eight studies show that gamma-glutamyl transpeptidase levels of the experimental group are lower than that of the control group ($Z = 2.04$, $P = .04$, MD = –4.05, 95% CI: [–7.96 to –0.15]). Thirteen studies show that triglyceride levels of the experimental group are lower than that of the control group ($Z = 4.15$, $P < .0001$, MD = –0.94, 95% CI: [–1.39 to –0.50]). Eleven studies show that the total cholesterol levels of the experimental group are lower than that of the control group ($Z = 5.42$, $P < .00001$, MD = –1.51, 95% CI: [–2.05 to –0.96]). Seven studies show that low-density lipoprotein-cholesterol levels of the experimental group are lower than that of the control group ($Z = 5.00$, $P < .00001$, MD = –0.85, 95% CI: [–1.18 to –0.52]).

Conclusion: Statins can significantly reduce liver biochemical indicators in patients with NAFLD.

Abbreviations: ALT = alanine aminotransferase, AP = alkaline phosphatase, AST = aspartate transaminase, CI = confidence intervals, CoA = coenzyme A, GGT = gamma-glutamyl transpeptidase, HCC = hepatocellular cancer, IR = insulin resistance, LDL-C = low-density lipoprotein-cholesterol, MD = mean difference, NAFLD = nonalcoholic fatty liver disease, NASH = nonalcoholic steatohepatitis, TC = total cholesterol, TG = triglyceride.

Keywords: meta-analysis, NAFLD, NASH, statins, systematic review

1. Introduction

Fatty liver diseases are divided into alcoholic fatty liver disease and nonalcoholic fatty liver disease (NAFLD). Fatty liver with alcohol intake >60 g/d (420 g/w) for men or >40 g/d (280 g/w) for women belongs to the category of AFLD. Fatty liver with alcohol intake of <20 g/d (140 g/w) for men or <10 g/d (70 g/w) for women is 1 diagnostic standard of NAFLD.[1] NAFLD is the most prevalent chronic liver disease.[2] It comprises NAFL, nonalcoholic steatohepatitis (NASH), advanced fibrosis, and cirrhosis. NAFL is a benign condition and NASH is its aggressive form.[3] The early symptoms of NAFLD are not obvious, and the disease progress is slow.[4] When it progresses to cirrhosis, NAFLD may rapidly cause hepatocellular cancer (HCC) or liver

This project was supported by the 2022 Scientific Research Project of Hunan Provincial Education Department (22C1372).

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 H, Toshiyoshi M, Zhao W, Zhao Y, Zhao Y. Statins on nonalcoholic fatty liver disease: A systematic review and meta-analysis of 14 RCTs. Medicine 2023;102:26(e33981).

Received: 7 February 2023 / Received in final form: 18 May 2023 / Accepted: 22 May 2023

http://dx.doi.org/10.1097/MD.0000000000033981

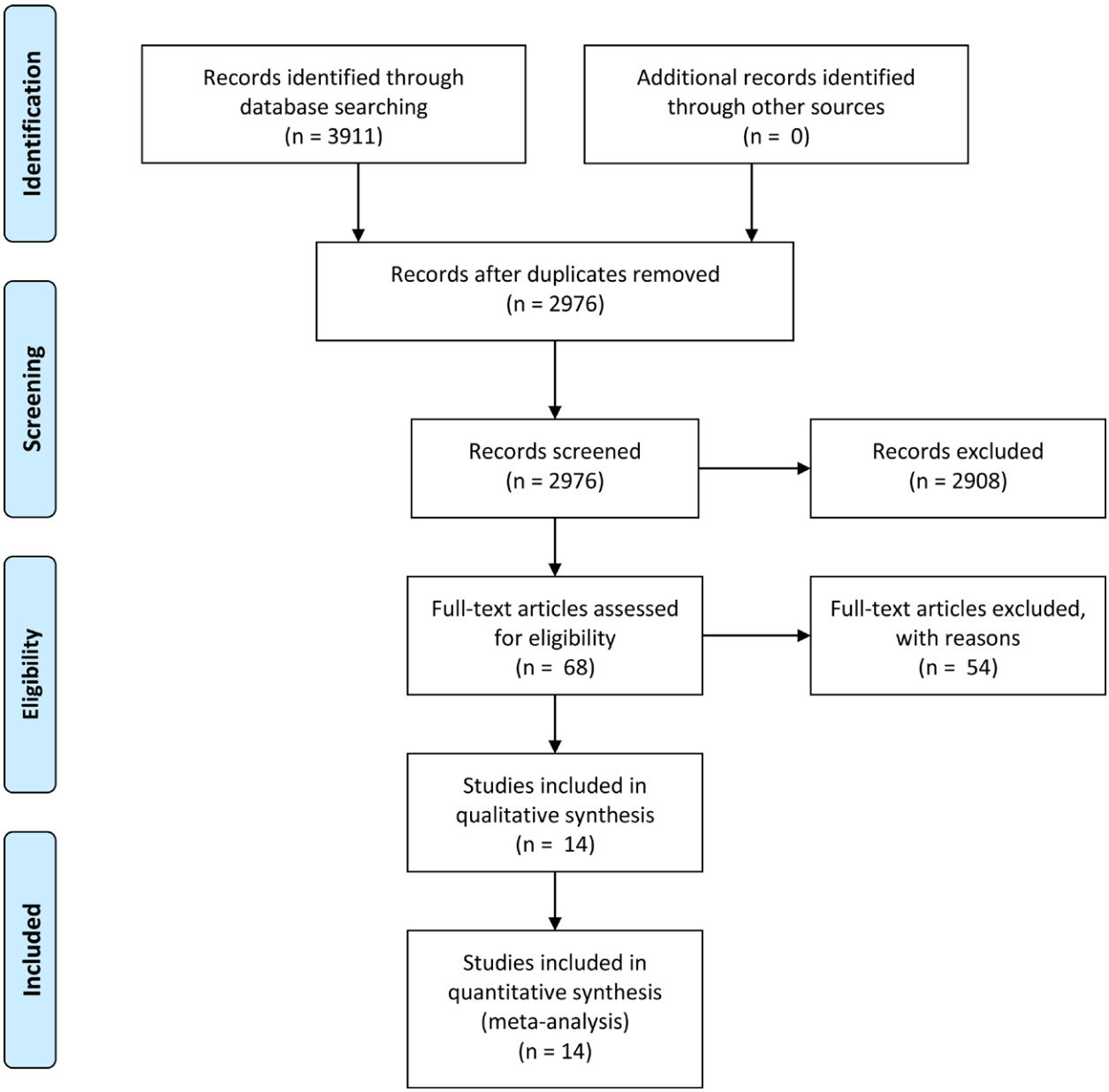

Figure 1. PRISMA 2009 flow diagram.

transplantation.[5] As a dynamic process, the etiology of NAFLD is complexly affected by many factors.[6]

Considering the development of NAFLD pathogenesis, the "multiple-hit theory has gradually replaced the "double-hit theory."[7] The first attack refers to vulnerable liver cells that come from an accumulation of fatty acids and triglycerides (TGs).[8] The second attack is the inflammatory cascade in hepatocytes. It may promote the occurrence and development of liver fibrosis.[9] Afterward, the third strike is to produce liver fibrosis during the hepatocytes' repair. The final strike is to cause microcirculation disturbance, ischemia, and hepatocyte necrosis. Then hepatic lobular reconstruction and cirrhosis may come up.[10] Liver fat accumulation, caused by obesity and insulin resistance (IR), represents an important "first hit."[11] Epidemiological studies show that type 2 diabetes mellitus and obesity are major risk factors for NAFLD.[12] The liver fat accumulation of NAFLD could originate from the IR, hyperinsulinemia, or excessive lipid availability.[13] IR enhances free fatty acids processed by the accumulation of adipose tissue in the liver. Hyperinsulinemia reduces the oxidation reaction of fatty acids in the liver. It increases the esterification reaction of free fatty acids, then may aggravate NAFLD in terms of the accumulation of TGs.[14] Improvement of IR can relieve metabolic syndrome, type 2 diabetes mellitus, and related complications. Meanwhile, reducing liver fat deposition is important. It is necessary to reduce the occurrence of cirrhosis, HCC, and its complications.[15]

Statins belong to the family of reductase inhibitors of hydroxymethylglutaryl coenzyme A (CoA). Statins prevent the conversion of hydroxymethylglutaryl CoA to methyldihydroxyvaleric acid, and then it reduces hepatic fibrosis or hepatocyte steatosis through a series of fat metabolism changes.[16] Based on an antioxidant function, statins can increase nitric oxide bioavailability, improve endothelial cell function, and affect hepatocyte fatty acid synthesis.[17] Statins also can improve the hepatic response to injury stimuli, regulate the bile acid pool size, reduce cholesterol levels, and inhibit the activation of cholesterol-modified receptors.[18]

The relationship between statins with abnormal lipid metabolism in NAFLD patients is not unambiguous, so we conducted a systematic review and meta-analysis of statins in the treatment of NAFLD.

Table 1

Basic information included in the literature.

Author	Year	Age	M/F	Duration (wk)	Treatment		Control		Patient/ diagnosis	Evaluation indicator
					Cases	Statins	Cases	Measures		
Joy[19]	2017	T: 56.7 ± 9.9 C: 54.7 ± 9.8	5/7	24	6	Sitagliptin 100 mg/d	6	Placebo	NASH/ Liver biopsy	ALT, AST, weight, TG, AP, BMI, GGT, HDL-C LDL-C
Nelson[20]	2009	T: 52.6 ± 8.6 C: 52.5 ± 13.0	11/5	48	10	Simvastatin 40 mg/d	6	Placebo	NASH/ Liver biopsy	ALT, AST, BMI, AP, TG, TC, LDL
Athyros[21]	2006	T: 59 ± 13 C: 61 ± 12	80/43	54	61	Atorvastatin 20 mg/d +Fenofibrate +RT	62	Fenofibrate +RT	NAFLD/ Liver biopsy and ultrasonography	Weight, ALT, AST, GGT, AP, TG, TC, LDL-C, HDL-C
Alam[22]	2018	T: 41.7 ± 9.1 C: 35.5 ± 6.9	12/28	48	20	Sitagliptin 100 mg/d +RT	20	RT	NASH/ Liver biopsy	ALT, AST, GGT, BMI, Weight, TG, LDL, HDL, AP
Samy[23]	2011	46.6 ± 5.56	22/28	32	25	Atorvastatin 40 mg/d + RT	25	RT	NAFLD/ Liver biopsy and ultrasonography	TG, TC, LDL, HDL
Smits[24]	2016	T: 61.5 ± 1.7 C: 65.8 ± 1.4	27/7	12	17	Sitagliptin 100 mg/d	17	Placebo	NAFLD/ Liver biopsy	HbA1c, Weight, BMI, ALT, AST, AP, GGT
Peng[25]	2013	T: 48.63 ± 5.24 C: 48.37 ± 6.03	45/35	24	40	Simvastatin 40 mg/d + RT	40	RT	NAFLD/ Liver biopsy and Ultrasonography	Total effective rate TG, TC,
Xu[26]	2015	35–64	65/25	12	45	Lovastatin 20 mg/d + RT	45	RT	NAFLD/ Ultrasonography	ALT, GGT, TG, TC, Total effective rate
You[27]	2011	24–64	86/29	16	57	Atorvastatin 20 mg/d + RT	58	RT	NAFLD/ Ultrasonography	TG, TC, LDL-C, HDL-C Total effective rate
Bi[28]	2016	T: 58.47 ± 2.51 C: 58.54 ± 2.46	66/34	24	50	Atorvastatin 20 mg/d + RT	50	RT	NAFLD/ Ultrasonography	ALT, AST, TG, TC, LDL-C, HDL-C, BMI, HbA1c
Qin[29]	2013	T: 51.50 ± 10.20 C: 52.20 ± 9.60	89/29	24	61	Atorvastatin 20 mg/d + RT	57	RT	NAFLD/ Ultrasonography	BMI, ALT, AST, FPG, TG, TC, LDL-C, HDL-C
Lai[30]	2012 C: 48.59 ± 11.97	T: 48.71 ± 11.02	58/2	36	30	Simvastatin 10 mg/d	30	Placebo	NAFLD/ Ultrasonography	ALT, AST, GGT total effective rate
Jiang[31]	2018	T: 44.62 ± 8.14 C: 43.64 ± 7.84	51/37	12	44	Fluvastatin 40 mg/d + RT	44	RT	NAFLD/ Ultrasonography	ALT, AST, TC, TG, BMI, Total effective rate, LDL-C, HDL-C
Li[32]	2011	21–60	48/32	12	40	Atorvastatin 10 mg/d + RT	40	RT	NAFLD/ Ultrasonography	ALT, AST, GGT, TG, TC, LDL-C, HDL-C

ALT = alanine aminotransferase, AP = alkaline phosphatase, AST = aspartate transaminase, BMI = body mass index, GGT = gamma-glutamyl transpeptidase, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol, NAFLD = nonalcoholic fatty liver disease, NASH = nonalcoholic steatohepatitis, TC = total cholesterol, TG = triglyceride.

Table 2

Quality evaluation of included literatures.

Included studies	Random allocation	Allocation concealment	Double-blind method	Evaluation of blindness	Data integrity	Selective report	Others
Joy 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Nelson 2009	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Athyros 2006	Unclear	Low risk	High risk	Unclear	Unclear	Unclear	Unclear
Alam 2018	Low risk	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear
Samy 2011	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Smits 2016	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear
Peng 2013	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear
Xu 2015	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear	Unclear
You 2011	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Bi 2016	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear
Qin 2013	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear
Lai 2012	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Jiang 2018	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Li 2011	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk

2. Methods

2.1. Article search strategy

All published articles were searched, from the earliest to January 2023, on the National Library of Medicine, Cochrane Library, China National Knowledge Infrastructure, Wanfang Data Knowledge Service Platform databases, and Web of Science. There was no limitation to languages.

2.2. Inclusive criteria

(1) Randomized controlled trials were selected.

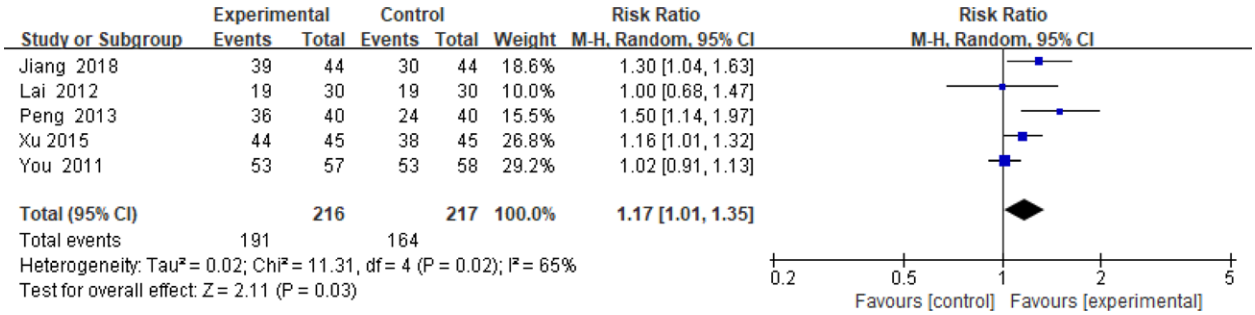

Figure 2. Changes in the total effective rate of the experimental group compared with the control group.

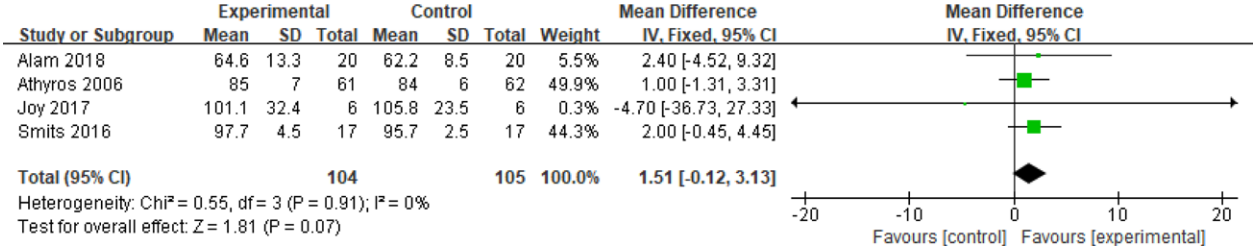

Figure 3. The experimental group compared with the control group in weight changes after treatment.

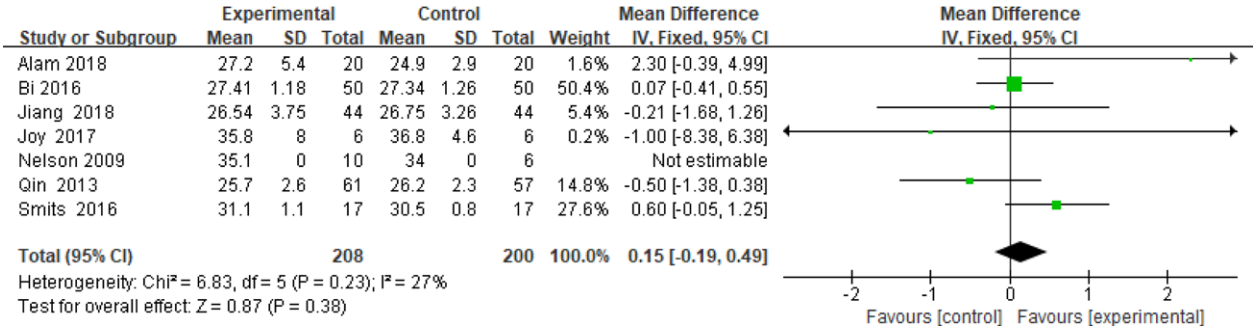

Figure 4. The experimental group compared with the control group in BMI changes after treatment. BMI = body mass index.

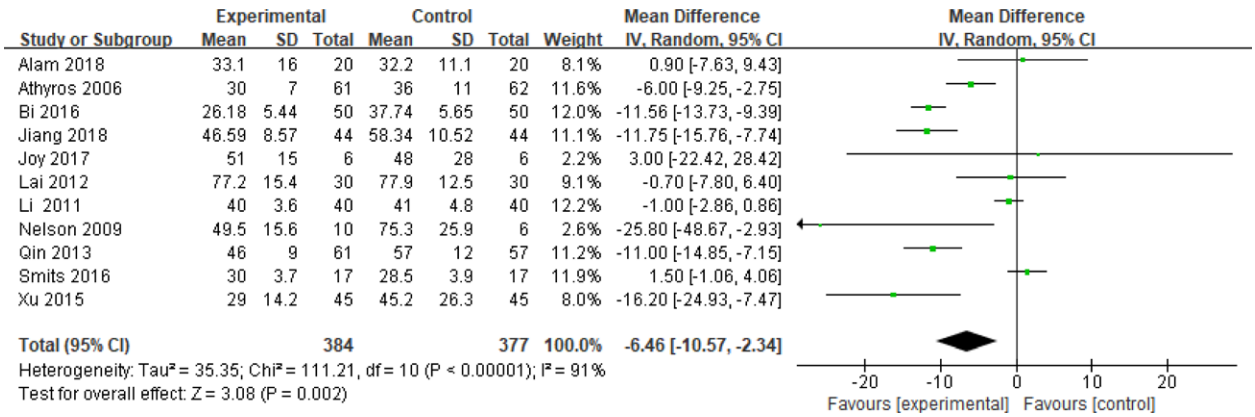

Figure 5. The experimental group compared with the control group in ALT changes after treatment. ALT = alanine aminotransferase.

(2) The patients included in the literature meet the diagnostic criteria of NAFLD.
(3) The control group received standard treatment, whereas the experimental group received a certain dose of statins and standard treatment.
(4) Outcome indicators are total effective rate, weight, alanine aminotransferase (ALT), aspartate transaminase (AST), body mass index, gamma-glutamyl transpeptidase (GGT), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol, TG, total cholesterol

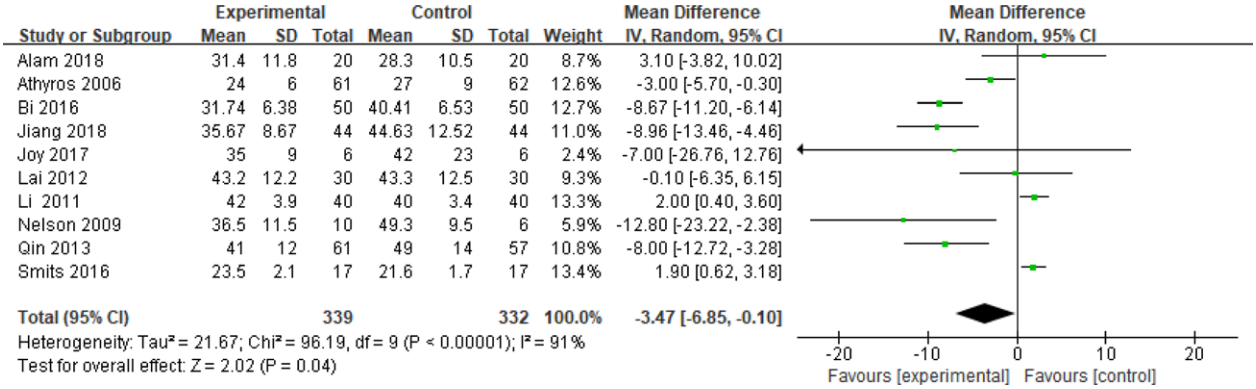

Figure 6. The experimental group compared with the control group in AST changes after treatment. AST = aspartate transaminase.

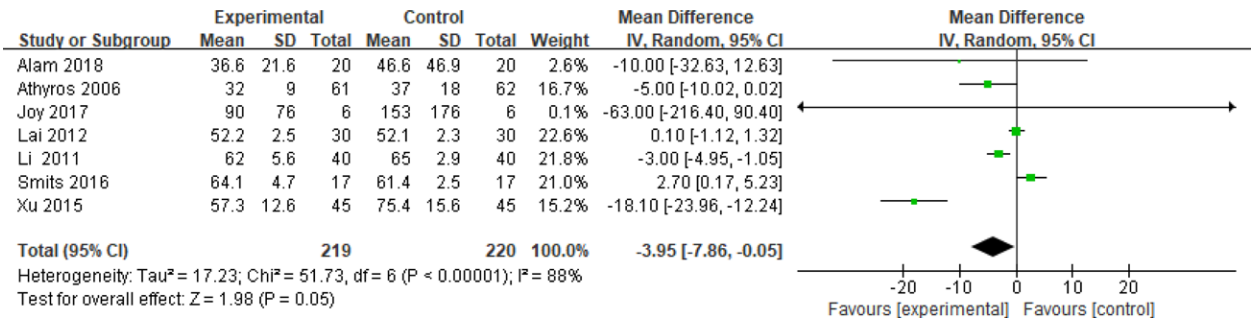

Figure 7. The experimental group compared with the control group in GGT changes after treatment. GGT = gamma-glutamyl transpeptidase.

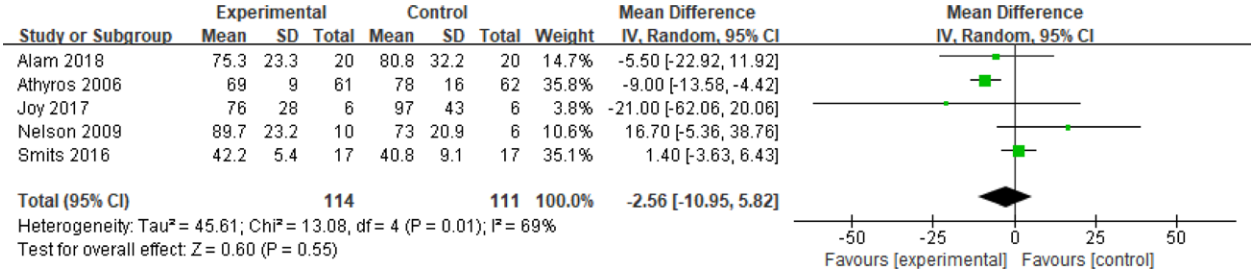

Figure 8. The experimental group compared with the control group in AP changes after treatment. AP = alkaline phosphatase.

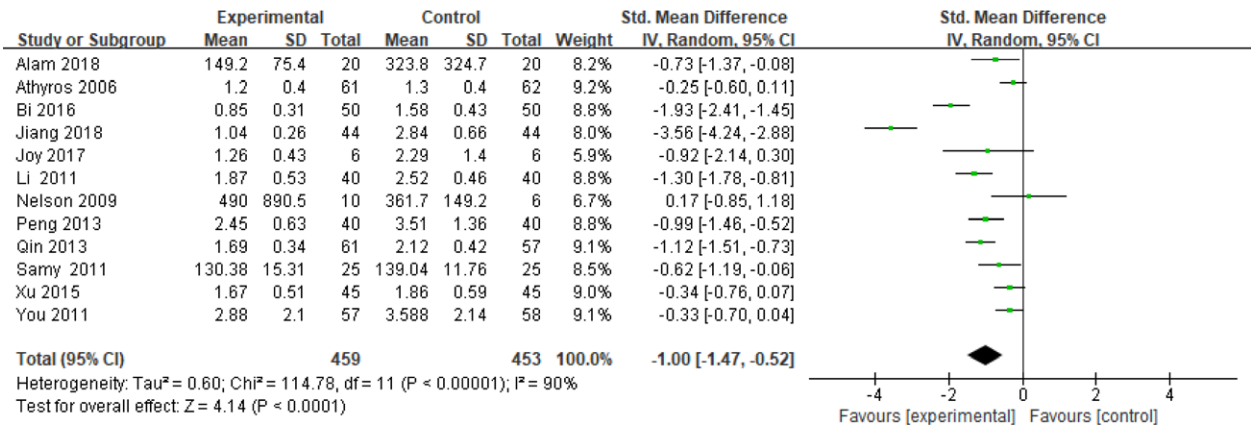

Figure 9. The experimental group compared with the control group in TG changes after treatment. TG = triglyceride.

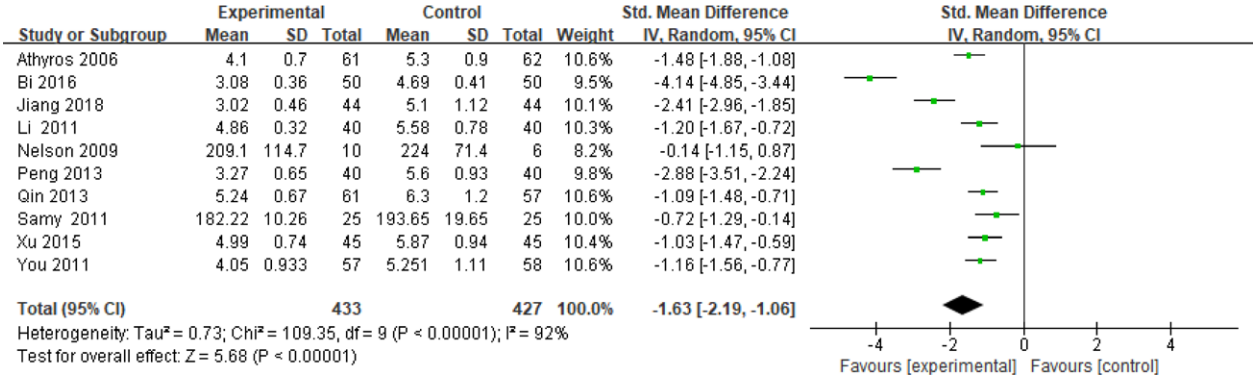

Figure 10. The experimental group compared with the control group in TC changes after treatment. TC = total cholesterol.

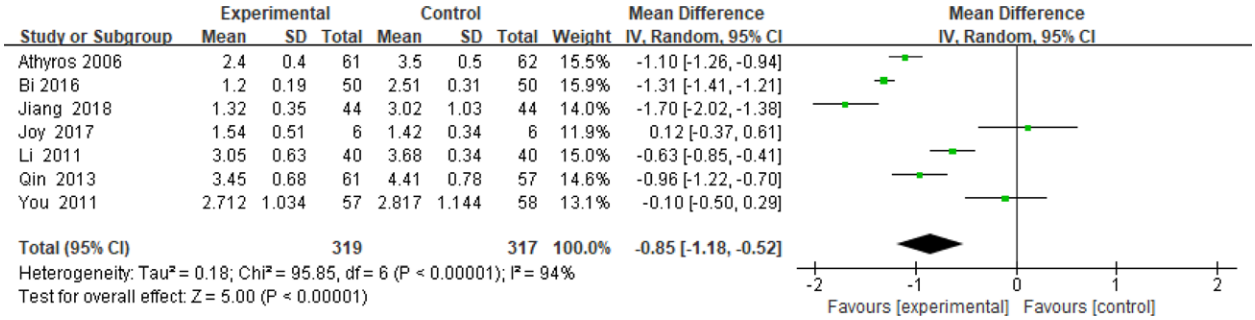

Figure 11. The experimental group compared with the control group in LDL-C changes after treatment. LDL-C = low-density lipoprotein-cholesterol.

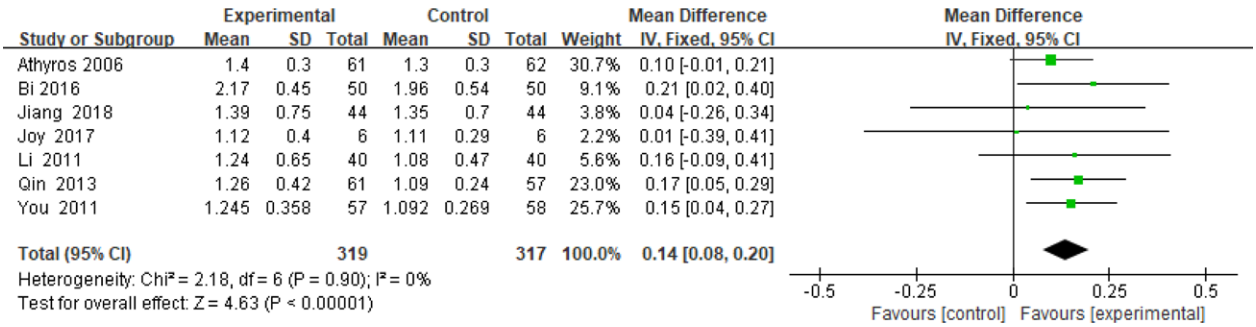

Figure 12. The experimental group compared with the control group in HDL-C changes after treatment. HDL-C = high-density lipoprotein-cholesterol.

(TC), and alkaline phosphatase (AP). For any abnormal sign or symptom, an adverse event has to be discussed.

2.3. Exclusion criteria

(1) Repeated references.
(2) Animal research or cell research.
(3) Literature that does not meet the requirements of this study.
(4) The design is not rigorous, such as the diagnosis and efficacy evaluation standards are not standardized, the sample data is not clear, and so on.

2.4. Quality evaluation and data extraction

The risk of bias was evaluated according to the Cochrane system evaluation tool. The evaluation content mainly includes 6 aspects: random allocation method; hidden allocation scheme; selective reporting of outcomes; blind method; incomplete outcome data; other potential sources of bias. According to the above 6 items, the included studies were evaluated for high risk of bias, low risk of bias, and unknown risk of bias.

2.5. Statistical analysis

Revman 5.3 software (Stata edition SE-16.0, Stata Corporation, College Station, TX) provided by Cochrane Collaboration Network is used for the meta-analysis. Data processing includes the heterogeneity test, the meta-analysis, and the publication bias analysis. For the included studies, the Q-statistic method is used for a statistical heterogeneity analysis. Heterogeneity test indicates that there is homogeneity among multiple similar studies ($P > .10$, $I^2 \leq 50\%$), and then the fixed effect model is used. If studies have heterogeneity ($P < .10$, $I^2 \geq 50\%$), the random effect model is used. For binary variables, the odds ratio and its 95% confidence interval (CI) are used. For continuous variables, mean difference (MD) is used. The standardized MD and its 95% CI are used for the statistical inference. $P < .05$ is considered to be statistically significant. Publication bias is analyzed by a funnel plot.

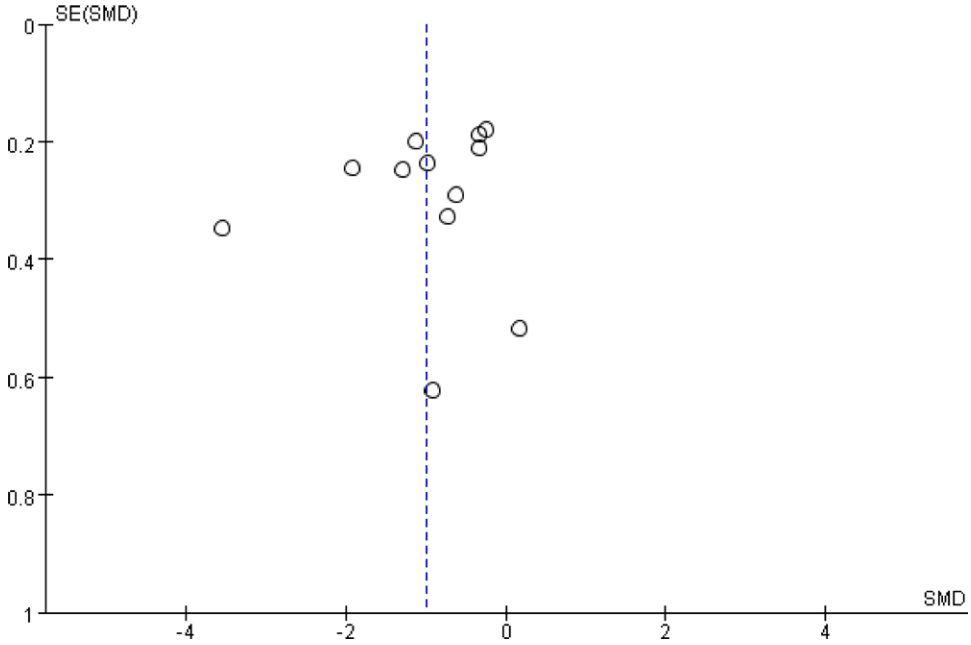

Figure 13. Funnel plot.

3. Results

3.1. Study selection

We identified 3911 trials, and there were 2976 records left after removing duplicates. According to the inclusion criteria, unqualified 2962 records were excluded. Finally, 14 eligible articles are included in the meta-analysis (Fig. 1).

3.2. Study characteristics and quality

The principal characteristics of the 14 trials are summarized in Table 1. Qualities are assessed according to Cochrane (Table 2). Most studies have low risk for all items, so the included studies are quality.

3.3. Meta-analysis of outcome

3.3.1. Total effective rate. Four hundred thirty-three patients of 5 articles are included in this assessment (216 in the experimental group and 217 in the control group). There is heterogeneity (P = .02, I^2 = 0.65), so the random effect model is used. It shows that the difference is statistically significant (Fig. 2). The effective rate of the experimental group is 17% higher than that of the control group (relative risk = 1.17, 95% CI: [1.01–1.35]).

3.3.2. Weight. Two hundred nine patients of 5 articles are included in this assessment (104 in the experimental group and 105 in the control group). Because there is no heterogeneity (P = .91, I^2 = 0%), a fixed-effects model is conducted. It shows that the difference is not statistically significant (Fig. 3).

3.3.3. Body mass index. Four hundred eight patients of 7 articles are included in this assessment (208 in the experimental group and 200 in the control group). There is small heterogeneity (P = .23, I^2 = 0.27), so a fixed-effects model is conducted. It shows that the difference is not statistically significant (Fig. 4).

3.3.4. ALT level. Seven hundred sixty-one patients of 12 articles are included in this assessment (384 in the experimental group and 377 in the control group). There is a large heterogeneity (P < .00001, I^2 = 0.91), so the random effect model is used. It shows that the difference is statistically significant (Fig. 5). The ALT level of the experimental group is lower than that of the control group (Z = 3.08, P = .002, MD = −6.46, 95% CI: [−10.57 to −2.34]).

3.3.5. AST level. Six hundred seventy-one patients of 11 articles are included in this assessment (339 in the experimental group and 332 in the control group). There is a large heterogeneity (P < .00001, I^2 = 0.91), so the random effect model is used. It shows that the difference is statistically significant (Fig. 6). The AST level of the experimental group is lower than that of the control group (Z = 2.02, P = .04, MD = −3.47, 95% CI: [−6.85 to −0.10]).

3.3.6. GGT level. Four hundred thirty-nine patients of 8 articles are included in this assessment (219 in the experimental group and 220 in the control group). There is a large heterogeneity (P < .00001, I^2 = 0.88), so the random effect model is used. It shows that the difference is statistically significant (Fig. 7). The GGT level of the experimental group is lower than that of the control group (Z = 1.98, P = .05, MD = −3.95, 95% CI: [−7.86 to −0.05]).

3.3.7. AP level. Two hundred twenty-five patients of 6 articles are included in this assessment (114 in the experimental group and 111 in the control group). There is a large heterogeneity (P = .01, I^2 = 0.69), so the random effect model is used. It shows that the difference is statistically significant (Fig. 8). The AP level of the experimental group is lower than that of the control group (Z = 0.60, P = .55, MD = −2.56, 95% CI: [−10.95 to 5.82]).

3.3.8. TG level. Nine hundred twelve patients of 13 articles are included in this assessment (459 in the experimental group and 453 in the control group). There is a large heterogeneity (P < .00001, I^2 = 0.90), so the random effect model is used. It shows that the difference is statistically significant (Fig. 9). The TG level of the experimental group is lower than that of the control group (Z = 4.14, P < .0001, MD = −1.00, 95% CI: [−1.47 to −0.52]).

3.3.9. TC level. Eight hundred sixty patients of 11 articles are included in this assessment (433 in the experimental group and

427 in the control group). There is a large heterogeneity ($P < .00001$, $I^2 = 0.92$), so the random effect model is used. It shows that the difference is statistically significant (Fig. 10). The TC level of the experimental group is lower than that of the control group ($Z = 5.68$, $P < .00001$, MD = −1.63, 95% CI: [−2.19 to −1.06]).

3.3.10. LDL-C level. Six hundred thirty-six patients of 7 articles are included in this assessment (319 in the experimental group and 317 in the control group). There is a large heterogeneity ($P < .00001$, $I^2 = 0.94$), so the random effect model is used. It shows that the difference is statistically significant (Fig. 11). The LDL-C level of the experimental group is lower than that of the control group ($Z = 5.00$, $P < .00001$, MD = −0.85, 95% CI: [−1.18 to −0.52]).

3.3.11. High density lipoprotein-cholesterol level. Six hundred thirty-six patients of 7 articles are included in this assessment (319 in the experimental group and 317 in the control group). There is no heterogeneity ($P = .90$, $I^2 = 0\%$), so the fixed-effects model is used. It shows that the difference is not statistically significant (Fig. 12).

3.3.12. Adverse reactions. Some patients have adverse events (4 patients for muscle weakness or pain, 9 patients for constipation, 15 patients for mild gastrointestinal reactions, 5 patients for abdominal pain, and 7 patients for abdominal distension). After treatment, all did not affect the following research. No serious adverse reaction was reported.

3.3.13. Publication bias. A funnel plot is applied to evaluate the publication bias of all 14 studies, and the bias is mild (Fig. 13).

4. Discussion

4.1. Efficacy analysis

Results demonstrate that statins have significant therapeutic effects on NAFLD. Our study shows that excessive fat deposition plays a key role in hepatocyte cytolysis and intrahepatic cholestasis. It is also reported that excessive fat deposition in hepatocytes leads to hepatocyte dysfunction and liver tissue injury in NAFLD patients.[33] In this research, the result shows that liver echo gradually returned to normal. It indicates a correlation between biochemical betterment and improvement of liver echogenicity and/or liver fibrosis, which is the parameter most influential on the prognosis in NAFLD/NASH patients, after statins' treatment. The index of liver fibrosis decreased in the results. Considering the known pharmacological mechanism, statins may involve in all stages of NAFLD. Because of an antioxidative stress function, statins can reduce collagenase activity and oxidized LDL in plaque lipids.[34] The decreasing endothelin function of statins improves IR[35]; then hepatic steatosis alleviates.[36] Statins elevate the β-oxidative activity of fatty acid B_2 while activating the oxidase activity of fatty acyl CoA.[37] As a consequence, shrinkage of plasma-free fat suppresses the inflammatory response.[38] Statins can alleviate collagen deposition, inhibit the formation of lipid peroxides, and then inhibit the progression of liver fibrosis.[39]

4.2. Limitations

Although the design is reasonable, our study has some limitations. Firstly, some studies may have unclear details in the randomized block, the randomization concealment, or the blinding method. All may lead to bias. Secondly, considering the characteristics of NAFLD, a long-term follow-up is needed. Finally, the total count of literatures and samples is small. Statins in the NAFLD management need further large-sample, multicenter, and quality randomized controlled trials.

4.3. Application prospects

Some studies found that insulin and sulfonylureas can increase the risk of NAFLD, whereas statin combination can alleviate this side effect.[40] NAFLD may progress to HCC, and it is an important cause of liver transplantation.[41] Doctors found that low-dose pravastatin or cerivastatin has a significant therapeutic effect on hyperlipidemia after liver transplantation and the safety is acceptable.[42] Statins may improve symptoms, suppress NAFLD development, and even prevent HCC or liver transplantation. The clinical applications of statins are worth further investigation.

5. Conclusion

Statins can significantly reduce liver biochemical indicators in patients with NAFLD.

Acknowledgments

The authors thank Dr Gengxin Wan for assistance with data extraction.

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