

Metabolic benefits of changing sedentary lifestyles in nonalcoholic fatty liver disease: a meta-analysis of randomized controlled trials

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Abstract: This study seeks to evaluate the effects of a reversal of sedentary lifestyles on the improvement of metabolic profiles in patients with NAFLD. The PubMed, Cochrane Library, Web of Science, and CNKI databases were searched up to May 15, 2021. Ten randomized controlled trials on changes in the sedentary lifestyle of patients with NAFLD were included in the analysis. Data from self-controlled case arms of randomized controlled trials investigating sedentary lifestyle alterations were extracted, and the effect size was reported as the MD and 95% CI. A total of 455 participants in 10 studies met the selection criteria. The results showed that changing a sedentary lifestyle can significantly improve ALT [MD = 4.35 (U/L), 95% CI: 0.53, 8.17], CHOL [MD = 0.31 (mmol/L), 95% CI: 0.19, 0.43], TG [MD = 0.22 (mmol/L), 95% CI: 0.10–0.34], LDL-C [MD = 0.30 (mmol/L), 95% CI: 0.02, 0.57], fasting blood glucose [MD = 0.17 (mmol/L), 95% CI: 0.03, 0.31], insulin [MD = 3.23 (pmol/L), 95% CI: 1.37–5.08], and HOMA-IR levels [MD = 0.39, 95% CI: 0.15, 0.63]. Changing sedentary lifestyle can also significantly improve body mass index (BMI) [MD = 1.12 (kg/m²), 95% CI: 0.66, 0.58], body fat (%) [MD = 0.34 (%), 95% CI: 0.13, 0.55] and VO_{2peak} levels [MD = -4.00 (mL/kg/min), 95% CI: -5.93, -2.06]. No differences in AST or GGT were noted before or after lifestyle changes. Altering a sedentary lifestyle to a lifestyle with regular exercise can slightly improve the levels of liver enzymes, blood lipids, blood glucose, insulin resistance, and body mass index in NAFLD patients.

Keywords: metabolism, nonalcoholic fatty liver disease, randomized controlled trial, sedentary lifestyle, self-controlled case series

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Introduction

Nonalcoholic fatty liver disease (NAFLD), which has been renamed metabolic associated fatty liver disease (MAFLD), has become the most prevalent chronic liver disease, affecting 26% of adults worldwide.^{1,2} The natural history of NAFLD demonstrates that the progression from the benign stage of simple steatosis to the progressive form of nonalcoholic steatohepatitis (NASH) with/without fibrosis is accompanied by worsening metabolism, such as weight gain, hyperlipidemia, and hyperglycemia. This phenomenon contributes to

increased risk of and death due to diabetes and atherosclerotic cardiovascular disease.^{3,4} Recently, it has been reported that 10–30% of NAFLD patients have NASH, and up to 25% of patients have significant liver fibrosis.³ Moreover, 1–2% of NAFLD patients have a more severe form of liver disease (cirrhosis, liver dysfunction and/or hepatocellular carcinoma).^{3,5}

A sedentary lifestyle is defined as insufficient energy expenditure and less than 1.5 metabolic equivalents (METs) due to low levels of physical

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activity.⁶ Population-based studies have demonstrated a dose-responsive association between the prevalence of NAFLD and sedentary time even after adjusting for obesity and other metabolic confounders.^{7,8} Moreover, given that no recognized pharmacotherapy is available for first-line treatment, lifestyle adjustment remains a critical component of the management of NAFLD and is recommended by guidelines from major societies.^{1,9} However, most studies reporting the beneficial effect of lifestyle intervention focused on NAFLD subjects overall, where the effects were similar among the subgroup with a sedentary lifestyle. The contribution of training types, intensity, and duration after changing sedentary behavior to exercise training remained undefined. This information is of particular clinical importance given that the previous meta-analysis including all NAFLD patients could potentially underestimate the beneficial effect of changing sedentary lifestyles.¹⁰ Identifying the metabolic benefit of changing sedentary lifestyle would be of clinical benefit because it may provide evidence to estimate whether the extent of physical activity would be sufficient to control metabolic abnormalities.

This study aimed to systematically review all self-controlled case series from randomized controlled trials evaluating the therapeutic effect of transition from a sedentary lifestyle to regular physical exercise to evaluate the effects of modifying lifestyle *via* exercise in patients with a confirmed sedentary lifestyle. A review of self-controlled case series may provide optimal evidence of therapeutic effects in the management of NAFLD.

Methods

The meta-analysis was designed, performed, and reported in accordance with the PRISMA statement¹¹ and Cochrane manual guidelines.¹²

Data sources and search strategy

This systematic review and meta-analysis design was registered in the PROSPERO registry, and the PROSPERO ID is 253581. We searched the PubMed, Cochrane Library, Web of Science, and China National Knowledge Infrastructure (CNKI) databases for randomized controlled trials investigating a change in the sedentary lifestyle of patients with NAFLD. The retrieval time was from the establishment of each database to May 15, 2021,

and the references of the included literature were manually searched. The following search terms were used: MAFLD, NAFLD, NASH, metabolic-related fatty liver disease, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, fatty liver, liver steatosis and hepatic steatosis, sedentary lifestyle, training, exercise, aerobic exercise, aerobic training, resistance exercise, resistance training, behavior, lifestyle, random controlled trial, random, and controlled trial.

Study inclusion and exclusion criteria

The inclusion criteria of the literature were randomized controlled trials with subjects who were confirmed to have NAFLD. The study population had a sedentary lifestyle before the trial, which was defined as physical activity less than 2 times/week for less than 20 minutes per session^{13,14} or less than 60 minutes/week of moderate intensity activity.¹⁵ The intervention measures were changing sedentary lifestyles and regular physical exercise. The data of the control group were obtained before the change in sedentary lifestyle. The outcome measures included liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyl transpeptidase (GGT)], blood lipids [total cholesterol (CHOL), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C)], glucose metabolism [fasting blood glucose (FBG), fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR)], and body mass index [BMI, body fat (%), VO_{2peak}].

The exclusion criteria for studies were the following: a diagnosis of NAFLD that did not meet the requirements; literature of investigation, description, or review; unclear experimental data or original data could not be obtained directly from the literature; and lack of statement of obtaining a signed informed consent.

Data extraction and quality assessment

Two researchers (Q.Q.M. and J.Z.Y.) independently screened and extracted data and evaluated the quality of the literature. The data that were consistent after cross checking between screening and extraction were included in the analysis, and those that were inconsistent were included after discussion with a third researcher. The basic information extracted included the name of the first author, year of publication, country, type of trial

design, intervention measures, follow-up time, monitoring indicators, NAFLD diagnosis method, and primary outcome. The extracted data included the mean, SD, and sample size of the relevant measures before and after the intervention. If essential information was missing, we contacted the author to obtain the missing information. This study included two types of interventions in the literature as two independent studies in the analysis.

Risk assessment of literature bias

According to the bias risk assessment tool recommended in the Cochrane 5.1 systematic review manual, Software Review Manager 5.3 was used to generate the quality assessment chart. The Cochrane bias risk assessment tool was used to evaluate the quality of the included literature. The evaluation included the generation of random sequences, allocation concealment, bias (blinding of the subjects and interveners as well as blinding of the result evaluators), incomplete result data, selective result reports, and other sources of bias. There were seven items in six categories. According to the overall assessment of bias risk, the literature was classified as high quality, general quality and low quality.

Statistical analysis

Data consolidation, heterogeneity testing, forest mapping, and subgroup analyses were performed using Software Review Manager Version 5.3. Sensitivity analyses were performed using Stata 12.0 software. The data were extracted as continuous variables, and the mean difference (MD) and 95% confidence interval (CI) were selected as the effect scales to merge the effect quantities. If $I^2 \leq 50\%$ ($p > 0.1$), there was no statistical evidence for severe heterogeneity or the heterogeneity was small. If $I^2 \geq 50\%$ ($p > 0.1$), the heterogeneity was high.

In our analysis, there were different intervention arms originating from a same study that were treated as separate studies, despite them being correlated. We performed a meta-analysis on all studies and subgroup analyses on different intervention groups. Because the value of a heterogeneity investigation is questionable when there are few studies, we used a random effects analysis for all studies, and we further performed sensitivity analyses by leaving out each study in turn to verify the robustness of the conclusions.

Results

Study characteristics and quality evaluation

A total of 902 articles were retrieved, and after reading abstracts and excluding repeated articles, 203 articles were obtained. A total of 190 nonrandomized controlled trials and studies of nondiagnosed NAFLD patients were excluded. After further reading, three articles were excluded. Finally, 10 articles were included in the analysis. The specific screening process is shown in Figure 1. The included information was compared with seven items of the Cochrane systematic review. Figure 2 shows that six studies had a low risk of bias in random sequence generation, five studies had a low risk of selection bias in information reported in allocation concealment, all studies had a high risk of bias because they were not blinded in participants or personnel, and all studies had a low risk of bias in incomplete outcome data and selective reporting. This experiment was a self-controlled study that focused on the changes in various indicators after the experimenter changed the sedentary lifestyle. This research did not involve blinded trials.

Basic characteristics of included studies

A total of 455 patients with NAFLD participated in and completed the included studies. Among them, three studies compared laboratory values before and after the intervention of aerobic exercise, six studies compared values before and after the intervention of aerobic exercise combined with resistance exercise, and one study compared values before and after the intervention of resistance exercise. Magnetic resonance imaging (MRI) and other imaging methods were used in all studies to confirm that the subjects had NAFLD. The therapeutic effect of lifestyle change was evaluated by measuring liver function indices (ALT, AST, and GGT), blood lipids (CHOL, TG, and LDL-C), glucose metabolism (FBG, insulin, and HOMA-IR) and body mass index [BMI, body fat (%), and VO_{2peak}] before and after the subjects changed from a sedentary lifestyle to a lifestyle with regular exercise. The basic characteristics of the included studies are shown in Table 1.

Effects of sedentary lifestyle changes on liver enzyme parameters

ALT, AST, and GGT are important biochemical indicators of liver function. Of the included

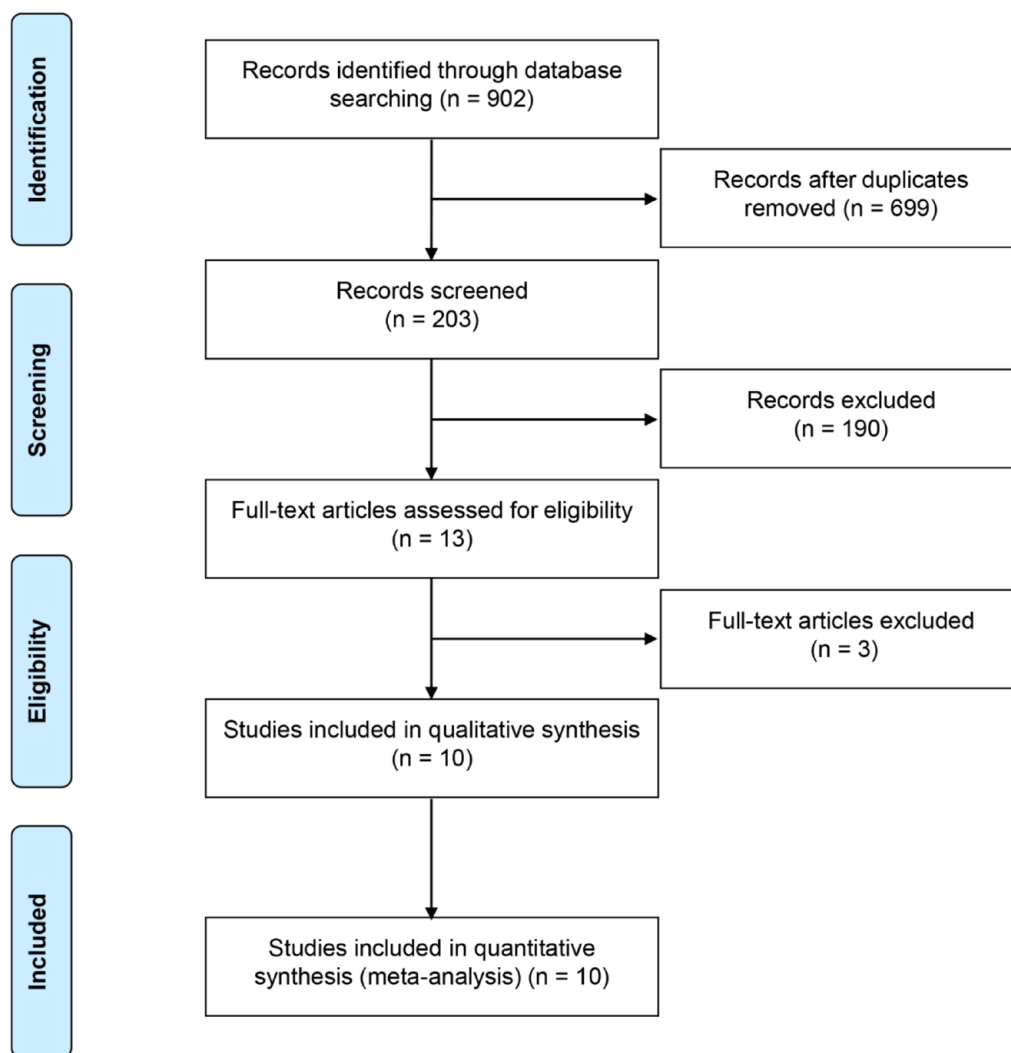


Figure 1. Flowchart of the study selection process.

studies, 8, 5, and 4 studies reported data on ALT, AST, and GGT, respectively. The meta-analysis showed that compared with a sedentary lifestyle, an exercise lifestyle could improve ALT levels [MD = 4.35 (U/L), 95% CI: 0.53, 8.17] (Figure 3(a)). Regarding GGT and AST levels, the effect was not significant [MD = 0.41 (U/L), 95% CI: -2.56, 3.39 and MD = 8.06 (U/L), 95% CI: -1.20, 17.33] (Figure 3(b) and (c)).

According to further classification of the exercise intervention duration, the subgroup analysis showed that patients with regular exercise for more than 12 weeks exhibited significant improvements in ALT levels [MD = 5.54 (U/L), 95% CI: 0.34, 10.75], but no significant improvements

in AST or GGT levels. When the total time of change to an active lifestyle was less than 12 weeks, ALT, AST, and GGT levels did not improve significantly (Supplementary Figure 1A, B and C).

Effects of sedentary lifestyle changes on blood lipid parameters

In the included literature, seven studies reported data on CHOL and TG levels for the blood lipid parameters, and three studies reported LDL-C levels. No significant heterogeneity in CHOL or TG levels (all $I^2 < 50\%$) was noted, but significant heterogeneity in LDL-C ($I^2 > 50\%$) was evident. Compared with a sedentary lifestyle, a regular exercise lifestyle can improve CHOL

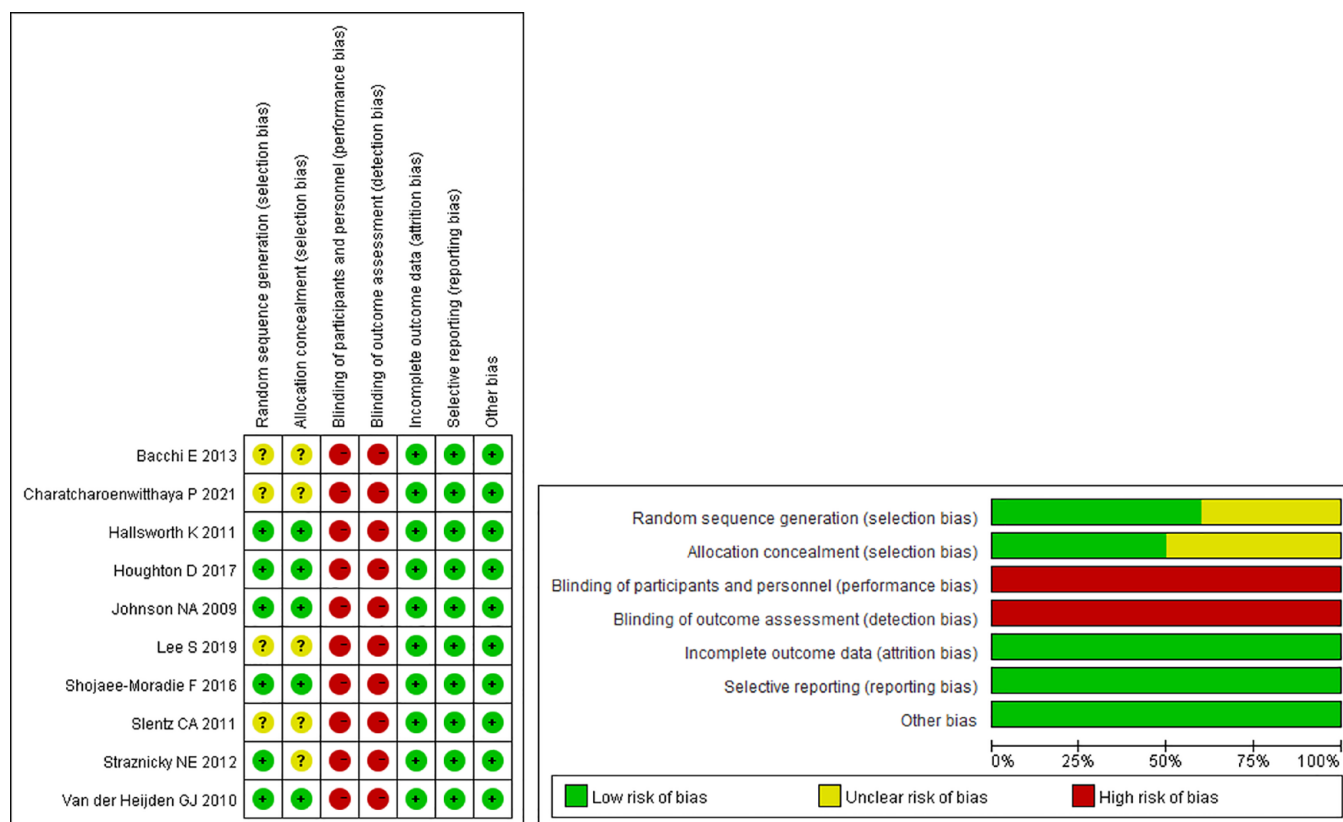


Figure 2. Methodological quality and risk of bias of the included trials.

[MD = 0.31 (mmol/L), 95% CI: 0.19, 0.43], TG [MD = 0.22 (mmol/L), 95% CI: 0.10, 0.34] and LDL-C levels [MD = 0.30 (mmol/L), 95% CI: 0.02, 0.57] (Figure 4(a)–(c)).

Regarding the duration of exercise intervention, the results of the subgroup analysis showed that patients with regular exercise could significantly improve the levels of CHOL [MD = 0.29 (mmol/L), 95% CI: 0.15, 0.43; MD = 0.39 (mmol/L), 95% CI: 0.09, 0.69] and TG [MD = 0.20 (mmol/L), 95% CI: 0.06, 0.34; MD = 0.29 (mmol/L), 95% CI: 0.05, 0.52] with exercise durations of both more than and less than 12 weeks (Supplementary Figure 2A and B).

Effects of sedentary lifestyle changes on blood glucose metabolism parameters

Eight, six and six studies reported data on FBG, insulin, and HOMA-IR levels, respectively. The heterogeneity among FBG, insulin, and

HOMA-IR studies was not significant ($I^2 < 50\%$). Meta-analysis showed that compared with a sedentary lifestyle, a regular exercise lifestyle could improve FBG [MD = 0.17 (mmol/L), 95% CI: 0.03, 0.31], insulin [MD = 3.23 (pmol/L), 95% CI: 1.37, 5.08] and HOMA-IR levels (MD = 0.39, 95% CI: 0.15, 0.63) (Figure 5(a)–(c)).

The subgroup analysis showed that compared with a sedentary lifestyle, aerobic therapy alone could significantly improve FBG levels [MD = 0.13 (mmol/L), 95% CI: 0.02, 0.24] (Supplementary Figure 3A). According to further classification of the exercise intervention duration, the subgroup analysis showed that patients with regular exercise for more than 12 weeks could significantly improve the levels of FBG [MD = 0.15 (mmol/L), 95% CI: 0.03, 0.26] and HOMA-IR (MD = 0.33, 95% CI: 0.06, 0.60), and HOMA-IR (MD = 0.63, 95% CI: 0.08, 1.19) could be improved with less than 12 weeks of exercise (Supplementary Figure 3B and C).

Table 1. Characteristics of the included studies.

Study	Year	Countries	Ethnicity	Participants	Control	Method NAFLD diagnosis	Study design and population	Subjects	Follow-up	Monitoring indicators	Outcome
Johnson <i>et al.</i> ¹⁶	2009	Australia	Caucasian	Obese	Aerobic exercise	MRS	Prospective population cohort	12	4 weeks	Hepatic, blood, abdominal and muscle lipid.	Regular aerobic exercise reduces hepatic lipids in obesity.
Van der Heijden <i>et al.</i> ¹⁷	2010	Hispanic	Caucasian	Obese	Aerobic exercise	MRI/MRS	Prospective population cohort	15	12 week	Visceral, hepatic, intramyocellular fat content and insulin resistance.	Aerobic exercise reduced hepatic and visceral fat accumulation, decreased insulin resistance.
Stentz <i>et al.</i> ¹³	2011	United States	Caucasian	Overweight	Aerobic training and resistance training	MRI	Prospective randomized trial	144	16 weeks	Visceral and liver fat, plasma liver enzymes, homeostasis model assessment.	Aerobic exercise is the most time efficient and effective exercise mode.
Hallsworth <i>et al.</i> ¹⁸	2011	United Kingdom	Caucasian	NAFLD; Overweight/obesity	Resistance exercise	MRI	Prospective randomized controlled trial	11	8 weeks	Liver lipid, glucose, HOMA-IR.	Resistance exercise specifically improves NAFLD.
Straznicky <i>et al.</i> ¹⁴	2012	Australia	Caucasian	Overweight/obesity	Caloric restriction together with exercise training	MRI	Prospective randomized controlled trial	22	12 week	ALT, GGT, insulin sensitivity, abdominal fat mass.	Exercise training did not confer significant incremental benefits.
Bacchi <i>et al.</i> ¹⁹	2013	Italy	Caucasian	Type 2 diabetes and NAFLD; Overweight/obesity	Aerobic training and resistance training	MRI	Prospective randomized controlled trial	31	16 weeks	Insulin sensitivity, body composition, hepatic fat content, subcutaneous abdominal adipose tissue.	Resistance training and aerobic training are equally effective in reducing hepatic fat content.
Shojaee-Moradie <i>et al.</i> ²⁰	2016	United States	Caucasian	NAFLD; Overweight/obesity	Aerobic exercise	MRI	Prospective randomized controlled trial	15	16 weeks	LDL, TG and apolipoprotein B.	After 16 weeks of exercise, LDL clearance increased and liver fat decreased.

(Continued)

Table 1. (Continued)

Study	Year	Countries	Ethnicity	Participants	Control	Method NAFLD diagnosis	Study design and population	Subjects	Follow-up	Monitoring indicators	Outcome
Houghton <i>et al.</i> ¹⁵	2017	Australia	Caucasian	NASH; Overweight/ obesity	Combined exercise	MRI	Prospective randomized controlled trial	12	12 weeks	Hepatic triglyceride content, body composition, inflammation markers, fibrosis, glucose tolerance.	12 weeks of exercise reduced hepatic triglyceride content, visceral fat and plasma triglyceride.
Lee <i>et al.</i> ²¹	2019	United States	Caucasian	Overweight/ obesity	Aerobic training and resistance training	MRI	Prospective randomized controlled trial	158	24 weeks	Insulin, glucose, liver fat.	Combined exercise and aerobic exercise alone are similarly beneficial in improving insulin sensitivity and reducing ectopic fat.
Charatcharoenwittaya <i>et al.</i> ²²	2021	Thailand	Asian	NAFLD	Aerobic or resistance exercise with dietary intervention	Transient elastography	Prospective randomized clinical trial	35	12 weeks	Transient elastography, anthropometry, body composition, cardiorespiratory fitness, biochemistries and glucose tolerance.	Aerobic and resistance training with dietary modification are equally effective for reducing intrahepatic fat and improving insulin resistance.

ALT, alanine aminotransferase; GGT, γ -glutamyl transpeptidase; HOMA-IR, homeostasis model assessment of insulin resistance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; LDL, low-density lipoprotein; TG, triglycerides.

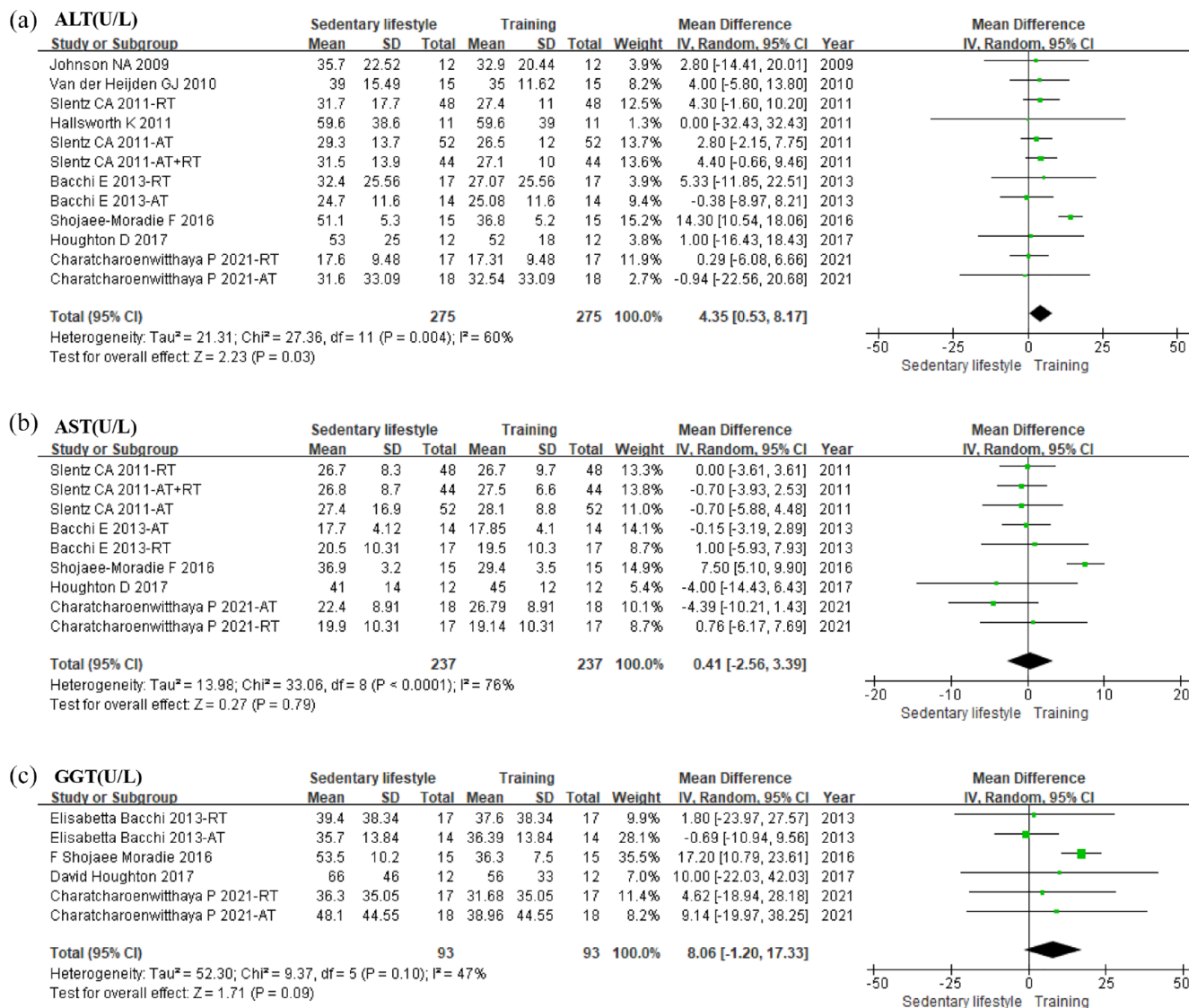


Figure 3. Meta-analysis of the effects of a sedentary lifestyle and training on hepatic enzyme parameters of NAFLD: (a) ALT (U/L), (b) AST (U/L), and (c) GGT (U/L).

Effects of sedentary lifestyle changes on body mass index

In total, nine, seven, and four studies reported data on BMI, body fat (%), and VO_{2peak}, respectively. No significant heterogeneity was noted between studies reporting BMI and body fat (%) (I² < 50%), but significant heterogeneity was noted between studies reporting VO_{2peak} (I² = 83%). The meta-analysis showed that compared with a sedentary lifestyle, a regular exercise lifestyle could improve BMI [MD = 1.12 (kg/m²), 95% CI: 0.66, 1.58], body fat (%) [MD = 0.34 (%), 95% CI: 0.13, 0.55], and VO_{2peak} levels

[MD = -4.00 (mL/kg/min), 95% CI: -5.93, -2.06] (Figure 6(a)–(c)).

The subgroup analysis showed that compared with a sedentary lifestyle, aerobic therapy alone could significantly improve BMI levels [MD = 1.05 (kg/m²), 95% CI: 0.51, 1.60] (Supplementary Figure 4A). The subgroup analysis also showed that patients with regular exercise for both more than and less than 12 weeks could significantly improve FBG [MD = 1.03 (kg/m²), 95% CI: 0.51, 1.56; MD = 1.38 (kg/m²), 95% CI: 0.45, 2.30] and VO_{2peak} levels [MD = -4.19

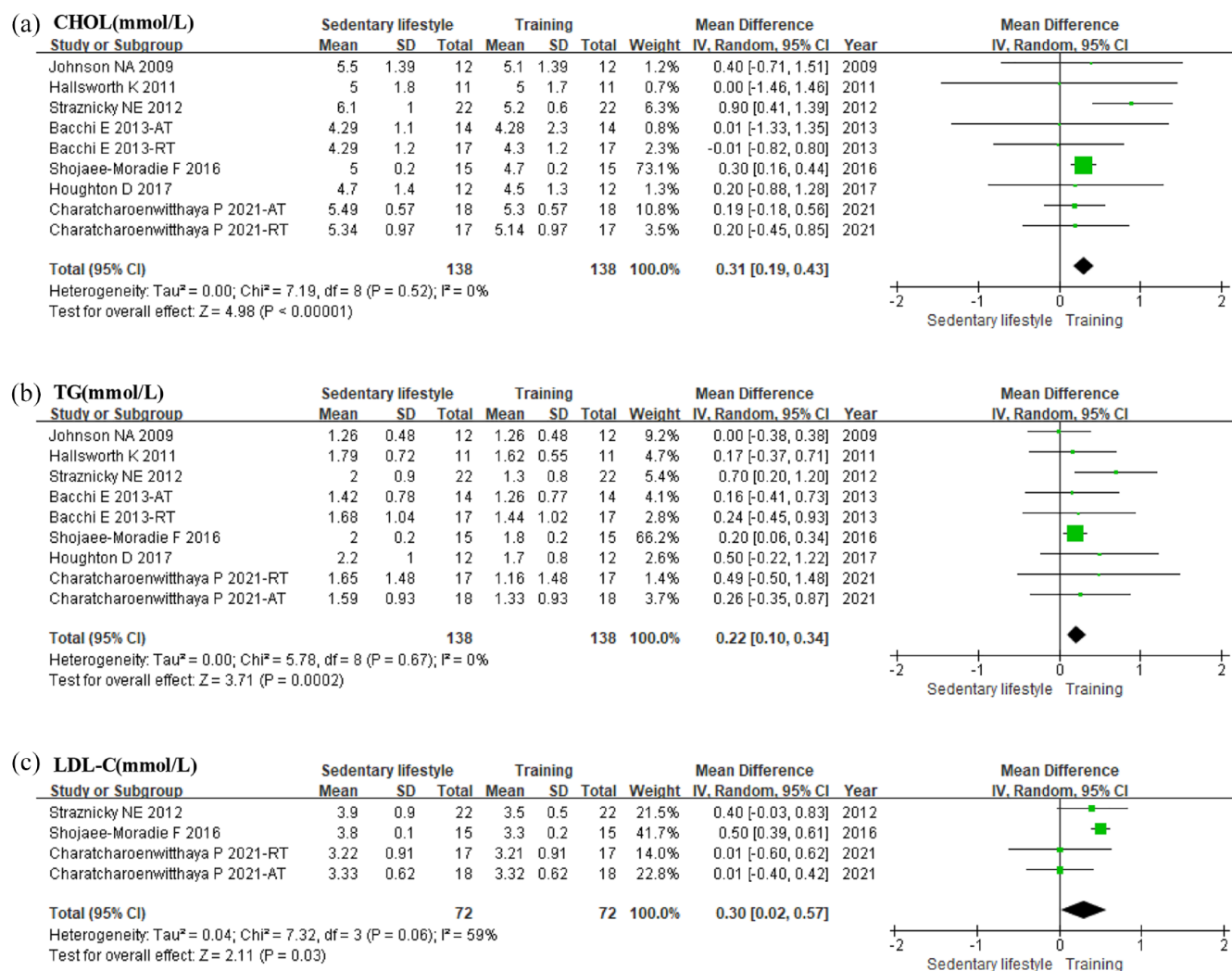


Figure 4. Meta-analysis of sedentary lifestyle and training serum lipid parameters of NAFLD: (a) CHOL (mmol/L), (b) TG (mmol/L), and (c) LDL-C (mmol/L).

(mL/kg/min), 95% CI: -7.20, -1.18; MD = -3.83 (mL/kg/min), 95% CI: -5.60, -2.07] (Supplementary Figure 4B and C).

Impact of relevant and independent studies on results

We conducted a subgroup analysis based on whether the studies came from a same article. Studies were considered to be correlated if they came from the same article. The subgroup analysis was not conducted for studies with less than three articles. Meta subgroup analysis showed that correlated and independent studies were consistent with the overall meta-analysis results

among ALT, BMI, and VO_{2peak} . In CHOL, TG, and FBG, the results from independent studies were consistent with the overall meta-analysis results, but correlated studies were inconsistent with the overall results. This may be due to different sample sizes or research methods, which needed further research (Supplemental Figure 5).

Sensitivity analysis and publication bias

We performed a sensitivity analysis to examine the stability of the pooled result. With the removal of individual studies from each analysis, the significance of the pooled results remained significantly consistent (Figure 7). Funnel plots of liver

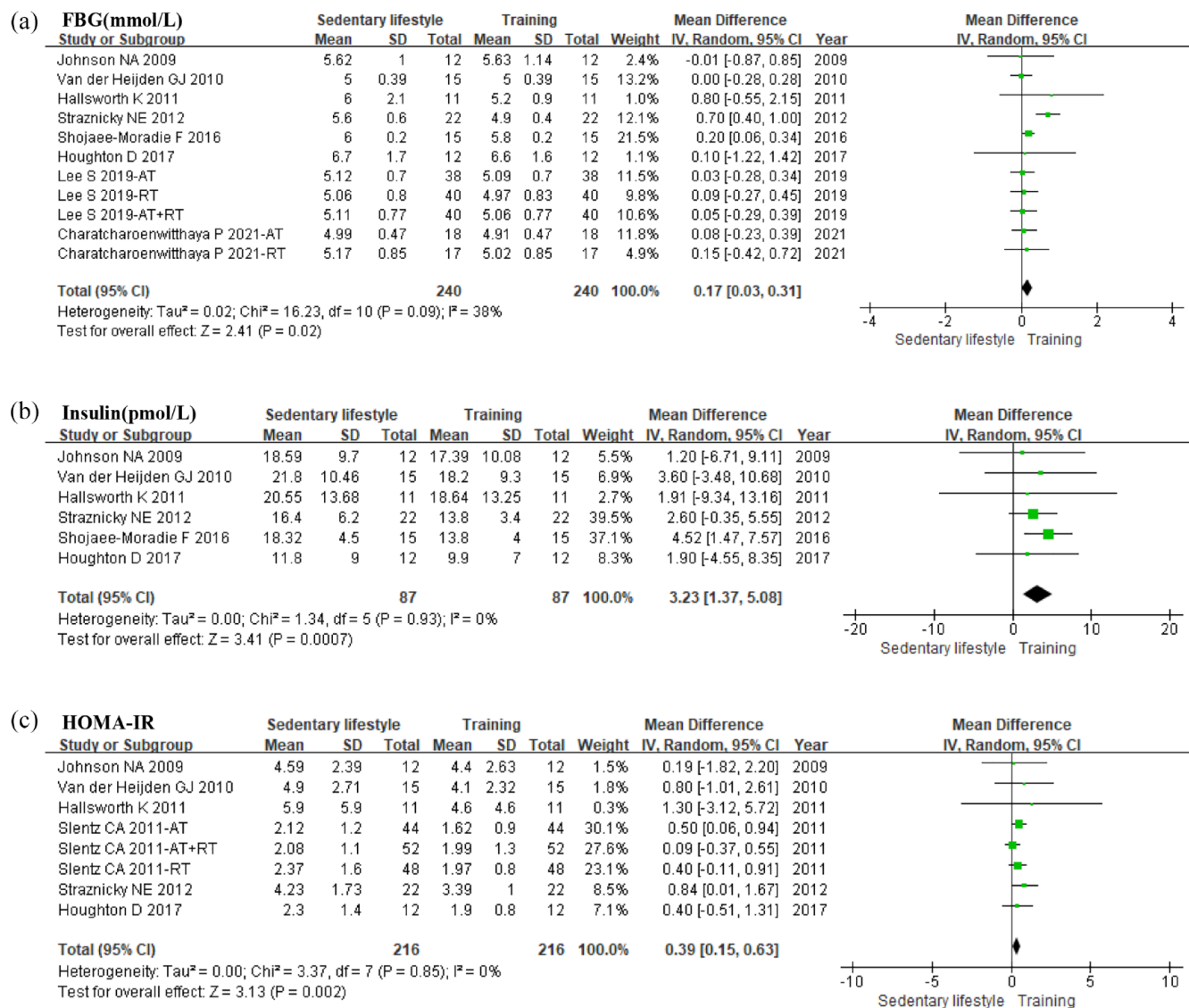


Figure 5. Meta-analysis of sedentary lifestyle and training on glucose metabolism parameters of NAFLD: (a) FBG (mmol/L), (b) Insulin (pmol/L), and (c) HOMA-IR.

function, blood lipids, blood glucose, and body mass index were generated to test publication bias (Figure 8). The research points of blood glucose and blood lipid metabolism were generally symmetrical, and the possibility of publication bias was low. Funnel plots of ALT and AST indicated that there might be publication bias (Figure 8(a) and (b)).

Discussion

Our meta-analysis results showed that changing an existing sedentary lifestyle to one with regular

exercise significantly improved the levels of alanine aminotransferase, total cholesterol, triglycerides, LDL-C, fasting blood glucose, insulin, insulin resistance, BMI, and VO_{2peak}. An exercise intervention duration longer than 12 weeks can significantly improve liver function, blood glucose, and lipid metabolism in NAFLD patients.

Hepatic manifestations of lipotoxicity may present as nonalcoholic steatohepatitis with liver injuries presenting as high levels of ALT, AST, and GGT. It has been described that normalization of liver injury markers was associated with

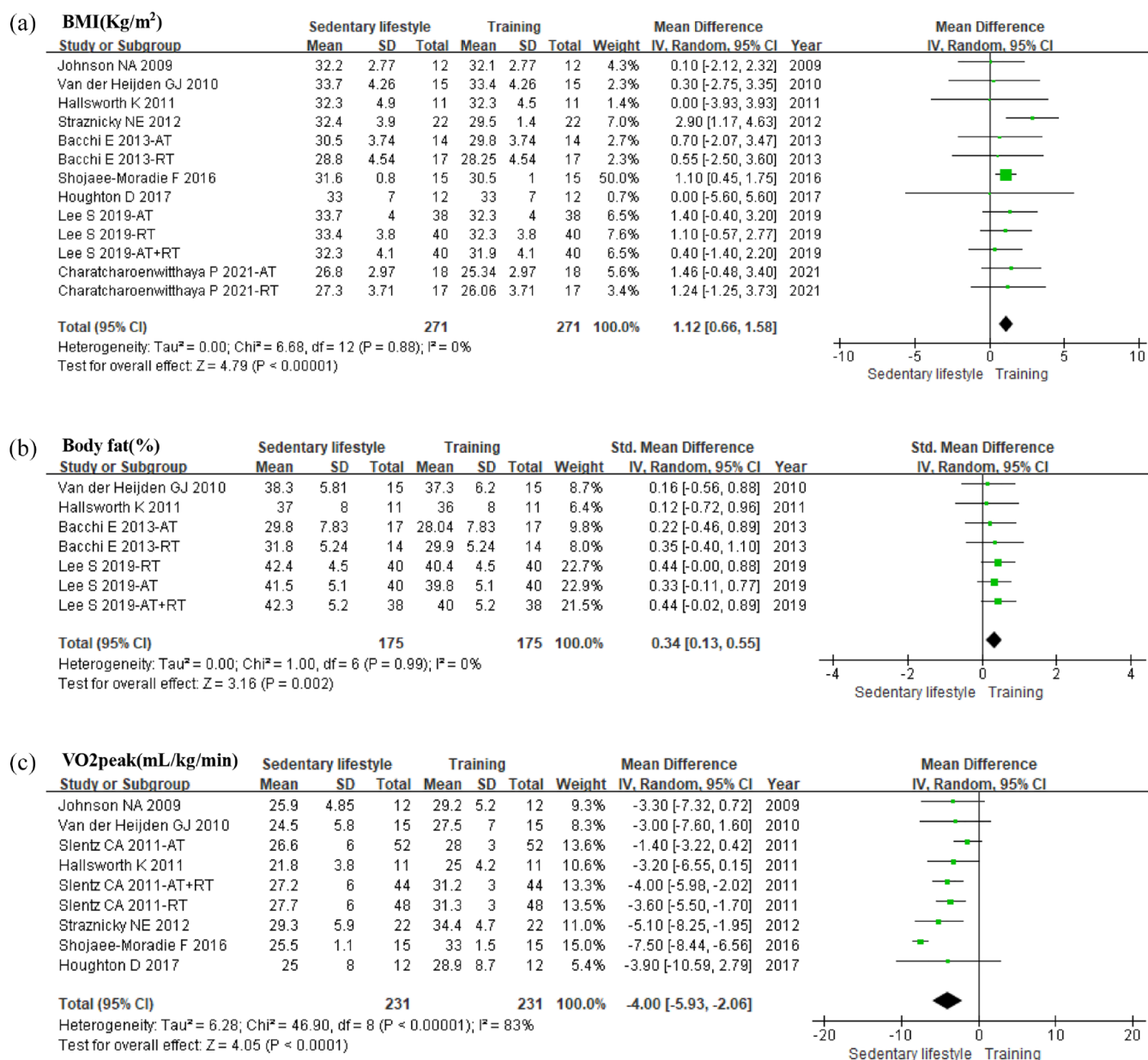


Figure 6. Meta-analysis of sedentary lifestyle and training on BMI, Body fat (%) and VO_{2peak} levels of NAFLD. (a) BMI (kg/m²), (b) Body fat (%), and (c) VO_{2peak} (mL/kg/min).

improvements in metabolic abnormalities.²³ Our findings further support that changing a sedentary lifestyle to one with regular exercise in patients with NAFLD can improve ALT but not GGT or AST liver enzyme levels, suggesting a potential limited beneficial impact on NASH and related metabolic abnormalities. One study examined the association between physical activity and NAFLD. In a recent paper from a Chinese NAFLD cohort with the majority of patients

undergoing lifestyle modification, the rate of GGT normalization was lower than that of ALT in those with concurrent abnormal ALT and GGT levels, and GGT normalization was associated with good control of weight and insulin resistance and considered a more reliable marker of NASH improvements.²³ Moreover, our subgroup comparison also confirmed that only those with intervention durations lasting for greater than 12 months would present improvement.

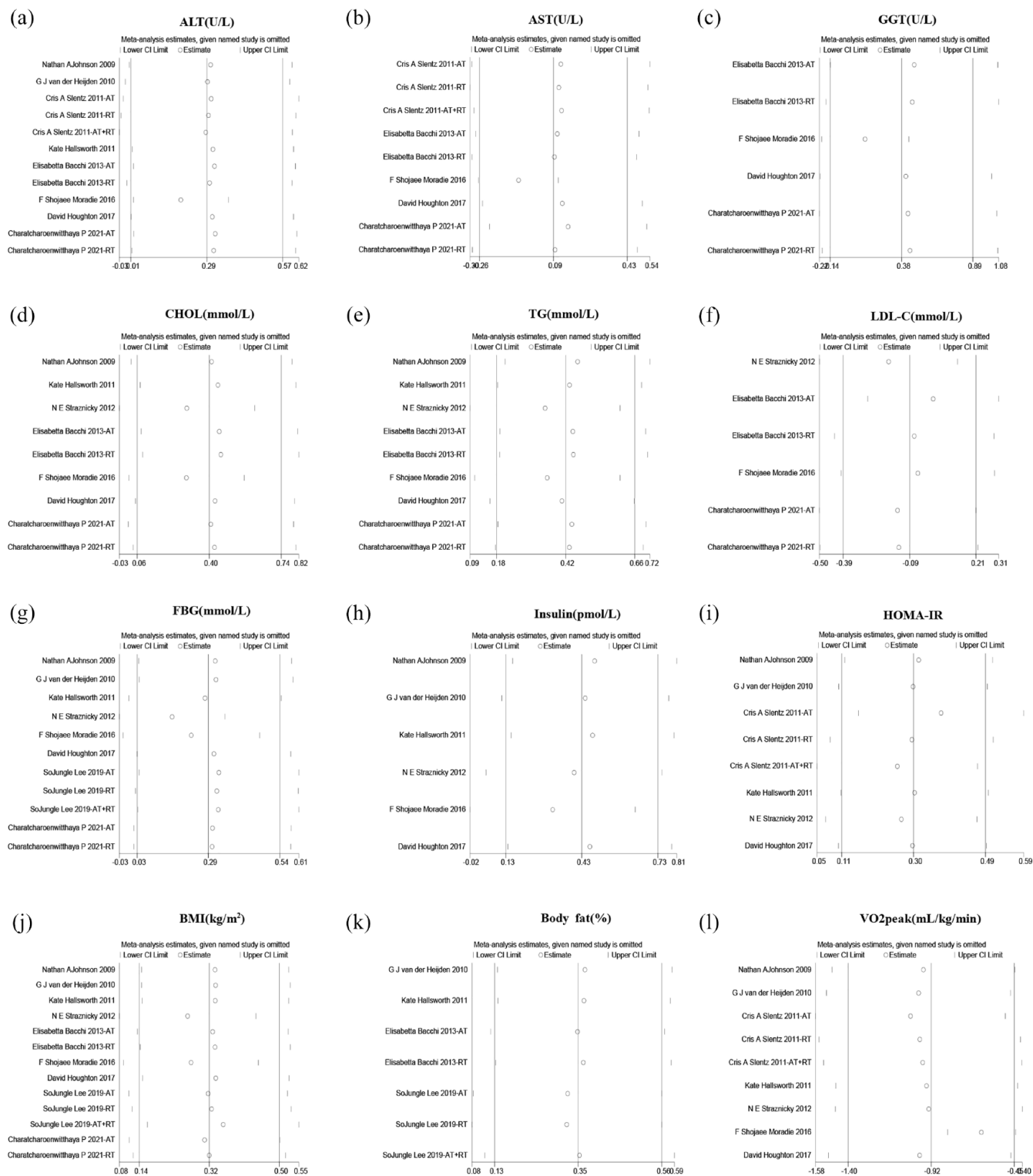


Figure 7. Sensitivity analysis of the included trials. (a) ALT (U/L), (b) AST (U/L), (c) GGT (U/L), (d) CHOL (mmol/L), (e) TG (mmol/L), (f) LDL-C (mmol/L), (g) FBG (mmol/L), (h) Insulin (pmol/L), (i) HOMA-IR, (j) BMI (kg/m²), (k) Body fat (%), and (l) VO_{2peak} (mL/kg/min).

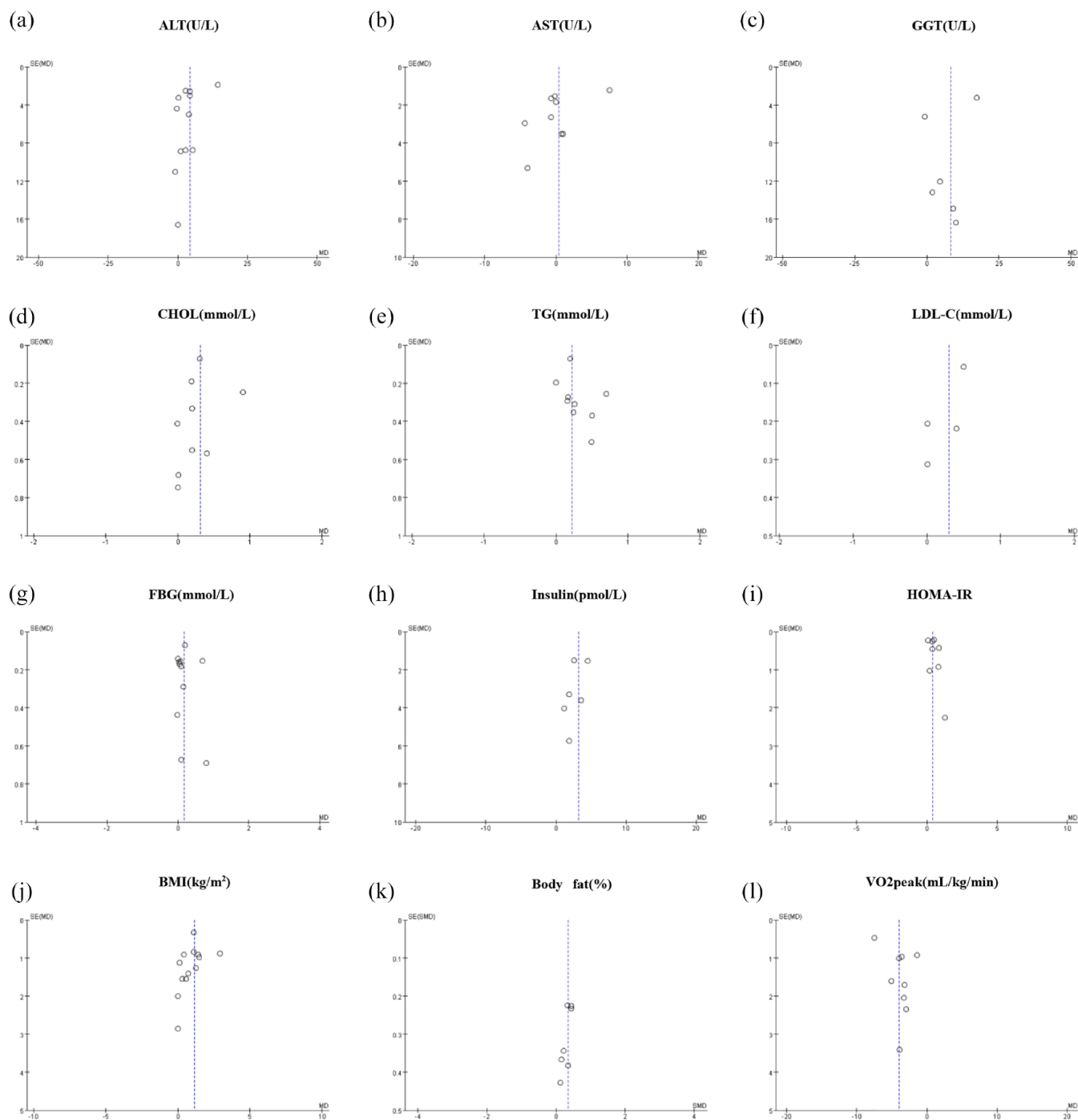


Figure 8. Funnel plot of publication bias of the included trials: (a) ALT (U/L), (b) AST (U/L), (c) GGT (U/L), (d) CHOL (mmol/L), (e) TG (mmol/L), (f) LDL-C (mmol/L), (g) FBG (mmol/L), (h) Insulin (pmol/L), (i) HOMA-IR, (j) BMI (kg/m²), (k) Body fat (%), and (l) VO_{2peak} (mL/kg/min).

Therefore, our results emphasized that exercise training may only play a mild protective role in NAFLD with a sedentary lifestyle, and this association requires at least a 1-year period.²⁴

Serum lipid parameters, including TG, CHOL, and LDL-C, have been identified as the predominant mediators of atherosclerosis.²⁵ Importantly, our study shows that changing a sedentary lifestyle

to a regular exercise lifestyle can significantly reduce all the above lipid levels despite varied types of training methods and durations.^{10,15} Although a statistically significant effect of lowering lipids in our meta-analysis results was found in the current research, the magnitude of the improvement by exercise treatments appears to be relatively small with values of 0.31 mmol/L CHOL [95% CI: 0.19, 0.43], 0.22 mmol/L TGs [95% CI: 0.10, 0.34], and 0.30 mmol/L LDL-C [95% CI: 0.02, 0.57] from the pooled results. The pooled results also demonstrated that an even longer physical activity intervention of more than 3 months had no significant effect on lipid metabolism. This finding was inconsistent with reports from a previous meta-analysis including patients with NAFLD not restricted to a sedentary lifestyle showing that long exercise durations correlated with better improvement effects of blood lipids.¹⁰ This finding needs to be further clarified by including more large randomized controlled trials (RCTs) given that only 4 RCT studies with training over 12 months were included for assessments.

As one of the most important pathogenic and metabolic comorbidity drivers, insulin resistance promoted progression to impaired glucose tolerance, type 2 diabetes mellitus (T2DM) and atherosclerosis in NAFLD patients. A previous meta-analysis demonstrated that sport training programs were effective in improving insulin resistance in overweight or obese individuals with decreased HOMA-IR (standardized mean difference = -0.34 [-0.49, -0.18], $p < 0.0001$, $I^2 = 48%$, 37 study).²⁶ Our results also showed that exercise can reduce insulin resistance estimated by HOMA-IR in patients with NAFLD. Several studies from Asia have found a dose-response relationship between weight loss and the improvement of steatohepatitis.²⁷ Even when body weight was reduced by only 3–5%, the liver histology of 40% of patients with NAFLD improved by varying degrees,²⁷ thereby counteracting hepatic and whole-body insulin resistance.

Study limitations

Our research has several limitations. First, the total number of included studies was small given that the literature review identified only a limited number of RCTs. Second, the majority of the population included in this study was Caucasian,

and the conclusions may not be applicable to the Asian population. Third, the data were extracted from secondary outcomes instead of at the individual level, which may cause some potential unknown biases. Fourth, in our analysis, different intervention groups from the same study were regarded as independent studies, but we did not fully involve the impact of this correlation on the results. Another issue that arises with analyzing many different outcomes and subgroups is inflated type I errors. The probability of obtaining at least one spurious statistically significant result was dramatically increased based on the number of tests that were performed in this meta-analysis.

Conclusions

In conclusion, changing a sedentary lifestyle to a lifestyle with regular exercise can significantly improve liver function, blood lipids, blood glucose, insulin resistance, and BMI in patients with NAFLD, but the extent of the improvements is moderate. The improvements in liver function, blood glucose, and lipid metabolism may depend on the duration of persistent training. In the future, we need to conduct larger and longer-term prospective randomized controlled trials to determine the long-term benefits and effects of a regular exercise lifestyle on patients with NAFLD.

Declarations

Ethics approval and consent to participate
Not Applicable.

Consent for publication
Not Applicable.

Author contributions

Qianqian Ma: Data curation; Formal analysis; Writing – original draft.

Junzhao Ye: Data curation; Formal analysis; Writing – original draft.

Congxiang Shao: Data curation; Investigation; Validation.

Yansong Lin: Data curation.

Tingfeng Wu: Data curation.

Bihui Zhong: Conceptualization; Funding acquisition; Project administration; Supervision.

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Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

None.

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Supplemental material

Supplemental material for this article is available online.

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