Physical activity intervention for non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is currently the most common cause of chronic liver disease. Diet and lifestyle changes have dramatically increased its prevalence worldwide. This meta-analysis was performed to investigate the efficacy of physical activity intervention on liver-specific endpoints in the NAFLD population, namely hepatic enzyme levels, serum lipid levels, and glucose metabolism.

Methods: PubMed and China National Knowledge Infrastructure (CNKI) databases were searched for randomized clinical trials of physical activity intervention on patients with NAFLD through to April 20, 2019. Effect sizes were reported as the standardized mean differences (SMD) and 95% confidence intervals (CI). The quality of the included studies was assessed using the Cochrane risk of bias tool. Meta-analyses were conducted using random-effect or fixed-effect models depending on the significance of heterogeneity. Clinical variability was investigated using subgroup analyses according to physical activity type and duration.

Results: Eleven studies with a cumulative total of 1000 participants met the selection criteria. Physical activity was associated with small reductions in three hepatic enzyme parameters: alanine aminotransferase, (SMD: -0.17, 95% CI: -0.29 to -0.05), aspartate aminotransferase, (SMD: -0.25, 95% CI: -0.37, -0.13), and γ -glutamyl transferase (SMD: -0.21, 95% CI: -0.35, -0.08). Significant small improvements were also found for total cholesterol (SMD: -0.22, 95% CI: -0.34, -0.09), triglycerides (SMD: -0.20, 95% CI: -0.32 to -0.07), and low-density lipoprotein cholesterol (SMD: -0.26, 95% CI: -0.39 to -0.13). Physical activity also slightly improved two glucose metabolism parameters: fasting glucose (SMD: -0.25, 95% CI: -0.37 to -0.12) and homeostasis model assessment of insulin resistance (SMD: -0.38, 95% CI: -0.52, -0.24). High-density lipoprotein cholesterol and fasting insulin between the physical intervention group and control group were not significantly different. Subgroup analysis suggested that both aerobic exercise alone and resistance exercise alone could improve most liver function and glucose metabolism outcomes and that longer exercise duration generally had better improvement effects. The difference between all subgroups was not significant, except for the TG subgroups categorized by physical activity type. **Conclusions:** Our findings suggest that physical activity alone can only slightly improve hepatic enzyme levels, serum lipid levels, and glucose metabolism in patients with NAFLD.

Background

Non-alcoholic fatty liver disease (NAFLD) is a multi-system disease characterized by fat storage and hepatic steatosis not caused by excessive drinking. NAFLD encompasses a wide histological spectrum ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), liver fibrosis, and cirrhosis, which can result in liver cancer. Currently, dramatic changes in the lifestyle and diet of the global population are causing a rapid increase in the prevalence of NAFLD parallel with that of obesity and diabetes [1]. It has been estimated that NAFLD will replace viral hepatitis as the primary factor of end-stage liver disease and liver transplantation by 2023 [2]. Currently, the prevalence of NAFLD worldwide is about 25.24%, with

prevalence being highest in South America and the Middle East (30.45–31.79%), followed by Asia, where the prevalence is approximately 27.37% [3]. Additionally, based on the result of one meta-analysis from mainland China, NAFLD prevalence in China is up to 45% [4]. NAFLD is becoming one of the most important public health issues in the world. The primary clinical treatment for NAFLD is lifestyle modification, which includes increasing physical activity and diet alteration [5]. Physical activity as a lifestyle modification plays an important role in the development of NAFLD, that it is inversely related with NAFLD risk [6–7]. However, clinical trials examining the therapeutic benefit of physical activity in NAFLD have reported inconsistent results [8–9], and the effectiveness and biological mechanism of physical activity, independent of diet, remain insufficient. Our objective, therefore, was to conduct a meta-analysis of the pooled data from published randomized controlled trials (RCTs) to evaluate the effectiveness of physical activity intervention on hepatic enzyme levels, serum lipid levels, and glucose metabolism in patients with NAFLD, which will provide substantial evidence on whether physical activity intervention has a favorable effect for treating NAFLD.

Methods

Data sources and search strategy

We performed a comprehensive search for English and Chinese language publications on the PubMed and China National Knowledge Infrastructure (CNKI) databases through to April 20, 2019. The search terms used were: physical activity, exercise, aerobic exercise, aerobic training, resistance exercise, resistance training, strength exercise, strengthening exercise, strength training, NAFLD, NASH, NAFL, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, fatty liver, liver steatosis, and hepatic steatosis. The reference lists of the selected articles and published reviews were manually searched to identify additional studies.

Inclusion and exclusion criteria

Two reviewers (Shu-Ting Wang and Jing Zheng) independently screened the literature selected from the initial search. Studies were included if they fulfilled the following inclusion criteria: (1) prospective RCT; (2) population of any age, sex, or ethnic origin with NAFLD diagnosed based on standard guidelines using non-invasive or invasive approaches; (3) intervention involving any type of physical activity with any intensity level or duration; (4) comparison with placebo (sham exercise) or usual care without physical activity; (5) outcomes of interest were improvements in hepatic enzymes, serum lipids, and glucose metabolism.

The exclusion criteria were: (1) only the abstract was available; (2) non-human study; (3) enrolled populations with secondary causes of fatty liver, such as alcohol, hepatitis viruses, or medication; (4) inclusion of patients with other metabolic issues, such as diabetes.

Data extraction and quality assessment

A pre-designed data collection form was used to extract the following information: first author, year of publication, country, trial design type, number of enrolled populations, participants' characteristics, intervention characteristics, duration of follow-up, and method of NAFLD diagnosis. If the articles contained insufficient information, we contacted the authors to obtain the missing details.

The methodological quality of each included study was assessed using the Cochrane risk of bias tool in Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark), which includes the following items: randomized sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The studies were classified into low, unclear, or high bias risk.

Two reviewers performed all data extraction and quality assessment independently. If discrepancies occurred, a consensus result was achieved by discussion.

Statistical analysis

The outcomes in this study are all continuous variables, presented as the standardized mean difference (SMD) and 95% confidence interval (CI). Heterogeneity was evaluated using the Cochran Q statistic and I^2 metric. A random-effect model was used to pool the study data if $I^2 > 50\%$, which represents statistical heterogeneity; otherwise, a fixed-effect model was used. As it is difficult to interpret the clinical effect size of the SMD [10], we used the interpretation thresholds proposed by Cohen et al., who suggested that $SMD < 0.2$, ≥ 0.2 and < 0.5 , ≥ 0.5 and < 0.8 , and ≥ 0.8 correspond to non-significant, small, moderate, and large effect size, respectively [11]. To investigate clinical variability, we conducted subgroup analyses based on physical activity type and duration. Further, sensitivity analyses were performed by removing each study individually to evaluate the stability and reliability of the primary meta-analysis results. When at least 10 studies were included in the meta-analysis, publication bias was detected using Egger's regression test, with $P < 0.05$ indicative of significance. All statistical analyses were conducted using R software 3.5.3.

Results

Literature search and study characteristics

Figure 1 shows the details of the literature search and study selection. Our search strategy initially identified 404 papers. Duplicate removal and screening through article title and abstract review identified 28 studies. Seventeen studies were excluded after the full text was reviewed. Finally, 11 studies involving 1000 participants were included in the meta-analysis [8–9, 12–20]. Among them, two studies [16,] [20] had more than one intervention group, therefore each intervention type was compared with the control group and analyzed. Table 1 outlines the characteristics of the included studies. The majority of the

included studies reported both male and female patients with NAFLD; only one involved only male patients [18]. All studies involved adult patients. The intervention duration was 8–48 weeks, with a median duration of 16 weeks (4 months).

Methodological quality

Figure 2 presents the methodological quality of the included studies. Most studies had low risk of bias in random sequence generation and allocation concealment; however, three studies had high risk in blinding of participants and personnel and only one study reported the use of blinding in outcome assessment. All studies had low risk of bias in incomplete outcome data and selective reporting.

Effect of physical activity on hepatic enzyme parameters

Eleven, ten, and eight studies reported data for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ -glutamyl transferase (GGT), respectively. The combined results suggested that physical activity alone could significantly improve the three hepatic enzymes: ALT (SMD: -0.17 , 95% CI: -0.29 to -0.05), AST (SMD: -0.25 , 95% CI: -0.37 , -0.13), GGT (SMD: -0.21 , 95% CI: -0.35 , -0.08), and heterogeneity among the studies was not significant ($I^2 < 50\%$). However, the effect size was generally small, with a marginal CI (Fig. 3).

Compared with no physical activity, subgroup analysis showed that aerobic exercise alone could significantly reduce AST (SMD: -0.26 , 95% CI: -0.43 , -0.10), but the effect size was small. However, aerobic exercise alone did not improve ALT and GGT. Resistance exercise alone had similar small improvement effects on the two enzymes: AST (SMD: -0.23 , 95% CI: -0.43 , -0.03), GGT (SMD: -0.24 , 95% CI: -0.44 , -0.03). However, the results regarding the combination of aerobic and resistance exercise showed no improvements for all three parameters. Heterogeneity between the subgroups was not significant (ALT, $P = 0.39$; AST, $P = 0.14$; GGT, $P = 0.93$) (Fig. 3).

Subgroup analysis according to intervention duration showed that, regardless of the type of physical activity, sustaining regular physical activity for >4 months could significantly improve hepatic enzyme levels, while <4 months' physical activity had no significant effect (Fig. 4).

Effect of physical activity on serum lipid parameters

Ten, nine, seven, and nine studies had sufficient data for inclusion in meta-analyses of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), respectively. There was no significant heterogeneity among these studies for these

four parameters ($I^2 < 50\%$). The pooled result showed that, compared with the control group, participants with regular physical activity were more likely to have slightly lower TC (SMD: -0.22 , 95% CI: -0.34 , -0.09), TG (SMD: -0.20 , 95% CI: -0.32 , -0.07), and LDL-C (SMD: -0.26 , 95% CI: -0.39 , -0.13). Physical activity tended to increase HDL-C levels as compared with the control, but the effect was not significant (SMD: 0.07 , 95% CI: -0.06 , 0.19) (Fig. 5).

In the subgroup analysis, resistance exercise alone could significantly reduce TC, but with a small effect size (SMD = -0.31 , 95% CI: -0.51 , -0.10), while neither aerobic exercise alone nor its combination with resistance exercise could improve TC. Heterogeneity between the subgroups was not significant ($P = 0.81$). Both resistance exercise alone and its combination with aerobic exercise could significantly reduce TG levels, with small (SMD: -0.32 , 95% CI: -0.52 to -0.11) and moderate (SMD: -0.59 , 95% CI: -1.06 to -0.12) effect size, respectively. However, aerobic exercise alone did not improve TG. There was no significant heterogeneity between the subgroups for TG ($P = 0.10$). The subgroup analyses also suggested that aerobic exercise alone and resistance exercise alone can significantly reduce LDL-C levels (SMD: -0.21 , 95% CI: -0.37 to -0.04 ; SMD: -0.35 , 95% CI: -0.56 to -0.15 , respectively), but the combination of aerobic and resistance exercise had no significant effect on LDL-C, which may due to the small sample size, as only one study was included in this subgroup. Heterogeneity between the subgroups was not significant ($P = 0.66$). All three subgroups showed non-significant results for HDL-C, and there was no difference between the subgroups ($P = 0.94$) (Fig. 5).

For duration of physical activity, both the ≥ 4 months and < 4 months groups had a significant effect on TC regardless of the type of physical activity (≥ 4 months, SMD: -0.19 , 95% CI -0.32 to -0.06 ; < 4 months, SMD: -0.40 , 95% CI -0.78 to -0.02). Similarly, both the ≥ 4 months and < 4 months groups had a significant effect on TG regardless of the type of physical activity (≥ 4 months, SMD: -0.16 , 95% CI -0.30 to -0.03 ; < 4 months, SMD: -0.48 , 95% CI -0.86 to -0.10). However, LDL-C reduction was significant only in the ≥ 4 months group (SMD: -0.25 , 95% CI: -0.38 to -0.12). Both subgroups showed a non-significant effect for HDL-C (Fig. 6).

Effect of physical activity on glucose metabolism parameters

Nine, six, and six studies had sufficient data for inclusion in analyses of fasting glucose, fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR), respectively. Heterogeneity among the studies for these three glucose metabolism parameters was not significant ($I^2 < 50\%$). The fixed-effect model showed that physical activity could reduce fasting glucose (SMD: -0.25 , 95% CI: -0.37 to -0.12) and HOMA-IR (SMD: -0.38 , 95% CI: -0.52 , -0.24). However, physical activity had no significant effect in improving fasting insulin (SMD: -0.18 , 95% CI: -0.45 , 0.10) (Fig. 7).

In the subgroup analysis, compared with the control, both aerobic exercise alone and resistance exercise alone could significantly reduce fasting glucose (aerobic exercise alone, SMD: -0.26 , 95% CI: -0.43 to $-$

0.10; resistance exercise alone, SMD: -0.27 , 95% CI: -0.47 to -0.06) and HOMA-IR (aerobic exercise alone, SMD: -0.42 , 95% CI: -0.63 to -0.22 ; resistance exercise alone, SMD: -0.34 , 95% CI: -0.54 to -0.13), but the two exercise types combined could not improve these two parameters. Heterogeneity between both subgroups for fasting glucose and HOMA-IR was not significant ($P = 0.07$ and $P = 0.11$ respectively). As for fasting insulin, the difference between subgroups was not significant (Fig. 7).

In the subgroup analysis according to intervention duration, significant improvements were found in the ≥ 4 months groups for fasting glucose and HOMA-IR. There was no significant effect for subgroup < 4 months on all three parameters (Fig. 8).

Sensitivity analysis and publication bias

Sensitivity analysis showed that the study by Jia et al. [20] could possibly influence the pooled results for fasting insulin and HOMA-IR. After excluding it, the pooled results for fasting insulin became significant (SMD: -0.36 , 95% CI: -0.69 to -0.02) and that for HOMA-IR became non-significant (SMD: -0.18 , 95% CI: -0.39 , 0.02), while the results for the other parameters were unlikely to be substantially altered.

Publication bias analysis was conducted when there were more than 10 included studies. Egger's test indicated statistically significant publication bias among the studies for ALT ($P = 0.043$).

Adverse events

Three studies [14, 19–] [19] [20] mentioned adverse events during the physical activity intervention. Among 1000 participants, two had knee pain, one had shoulder pain, one had back pain, and two had bone fractures that did not occur during the exercise sessions reported. Overall, the incidence of adverse events was quite low, suggesting that physical activity intervention was well-tolerated. However, only a few studies reported on adverse events, and the trials lasted 2–13 months. Therefore, further studies are needed to prove the long-term safety of physical activity intervention.

Discussion

In the present meta-analysis, we attempted to collect less biased evidence to identify the effect of physical activity intervention on patients with NAFLD. The 11 studies included suggested that physical activity intervention can improve hepatic enzyme levels, most serum lipid levels, and glucose metabolism, except HDL-C and fasting insulin, in patients with NAFLD. Although our meta-analysis results show a statistically significant effect, the magnitude of the improvement by physical activity intervention appears non-significant or small according to Cohen's rule of thumb. This differs from previous reviews reporting that physical activity can significantly improve hepatic enzyme and serum lipid levels with a moderate to large pooled effect size [22–23] [], but these previous studies included patients with NAFLD with diabetes, so the improvement may partly be due to antidiabetic medication or other treatment.

The mechanism of physical activity intervention benefiting patients with NAFLD remains unclear and there is no specific recommendation for the type of physical activity. The subgroup analyses showed that, compared with usual care without physical activity, both aerobic exercise alone and resistance exercise alone could improve most liver function and glucose metabolism outcomes, which is consistent with the results of a systematic review by Kenneally et al. [24]. This finding is important for patients with NAFLD with obesity, for whom resistance exercise is more appropriate, as some types of aerobic exercise may result in joint stress or injury. However, our results suggest that the combination of aerobic and resistance exercise was less effective, only improving TG and fasting insulin. This is probably due to the small sample size as the subgroup had only 76 participants in total. Longer exercise durations generally had better improvement effects, although the difference between subgroups was not significant. In the sensitivity analysis, we excluded the study by Jia et al. [20], and pooled results for fasting insulin became significant while that of HOMA-IR became non-significant, indicating that our results for glucose metabolism parameters are insufficiently robust. We believe that this could be due to the lack of statistical power, as only six of the included studies reported on fasting insulin and HOMA-IR.

To the best of our knowledge, this is the first systematic review to evaluate the comprehensive effectiveness of physical activity on hepatic enzyme levels, serum lipid levels, and glucose metabolism in western and Chinese patients with NAFLD. The study population was restricted to subjects with NAFLD without other chronic diseases that may have biased results, such as diabetes. We also excluded other factors that may have affected the meta-analysis results, such as diet adjustment or lipid-lowering medication.

Our study has several limitations. First, several of the included studies did not describe the intensity of the physical activity interventions clearly, therefore we could not perform subgroup analysis categorized by intensity, which may possibly influence the effect of the physical activity. Second, subgroup analysis according to different NAFLD diagnostic methods was inapplicable because Shojaee-Moradie et al. [18] used more than one diagnostic method for confirming NAFLD. However, differences in the sensitivity and specificity of the different diagnostic methods could result in clinical heterogeneity. Biochemical tests have low specificity, and ultrasound is less accurate for patients with mild steatosis. The sensitivity of magnetic resonance imaging (MRI) for diagnosing hepatic steatosis is slightly higher than that of ultrasound. Nevertheless, all imaging examinations cannot detect the degree of liver inflammation and necrosis. Only liver biopsy can identify NAFL and NASH [25]; among the non-invasive methods, ¹H-MRS (MR spectroscopy) is the most accurate [26]. Apart from that, the differing professional levels and clinical skills of the researchers in the included studies may also have affected the reported outcomes. In addition, among the included studies, the longest intervention duration was 48 weeks, therefore we could not determine the long-term benefit of physical activity. Another drawback is that although we searched the published studies thoroughly, we cannot rule out the possibility of missing unpublished studies with null effects, and we only included studies published in English and Chinese in this meta-analysis, which may explain the significant publication bias found for ALT.

Conclusions

Our meta-analysis suggests that regular physical activity, whether aerobic or resistance exercise alone, can improve hepatic enzyme levels, most serum lipid levels, and glucose metabolism parameters in patients with NAFLD, but the effect size is generally small. Therefore, the expectation of great improvement in NAFLD from physical activity alone needs to be tempered with caution. Future large-scale prospective RCTs are needed to determine the long-term benefits and safety of physical activity.

Abbreviations

NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; RCT: Randomized controlled trial; SMD: Standardized mean difference; CI: Confidence intervals; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ -glutamyl transferase; TC: Total cholesterol; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol

Declarations

Acknowledgements

Not applicable.

Author's Contributions

Study concept and design: PXE and WST; Collection and assembly of data: WST, ZJ, PHW and PXT; Data analysis and interpretation: CXL and LHQ; Manuscript writing and review: WST, ZJ and PXE. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Characteristics of the included studies

Study	Design	Enrolled Participants (n)	Intervention characteristics			Control	Method for NAFLD diagnosis	
			Physical activity type	Sessions per week	Intervention duration (weeks)			
Sullivan 2012 [12]	monocentre	18	Obese adults with NAFLD	Aerobic	5 times	16	Continue current activities of daily living	1H MRS
Pugh [8]	2013 monocentre	13	Adults with NAFLD	Aerobic	3-5 times	16	Basic lifestyle advice	Biochemical tests
Pugh [13]	2014 monocentre	31	Obese adults with NAFLD	Aerobic	3-5 times	16	Conventional care	MRI
Zelber-Sagi 2014 [14]	monocentre	82	Adults with NAFLD	Resistance	3 times	12	Sham exercise (stretching)	Ultrasonography
Hallsworth 2015 [15]	monocentre	23	Adults with NAFLD	Aerobic Resistance	+ 3 times	12	Standard care	MRI
Shamsoddini 2015 [16]	monocentre	30	Male adults with NAFLD	Aerobic +Resistance	135 min	8	No intervention	Ultrasonography
Cuthbertson 2016 [17]	monocentre	69	Adults with NAFLD	Aerobic	3 times	16	Conventional counselling	MRI
Shojaee 2016 [18]	monocentre	29	Male adults with sedentary lifestyles and NAFLD	Aerobic Resistance	+ 4-5 times	16	Standard care	Ultrasonography or Liver biopsy
Zhang [19]	2016 monocentre	220	Obese adults with NAFLD	Aerobic	150 min	48	No intervention	1H MRS
Houghton 2017 [9]	monocentre	24	Adults with sedentary lifestyles and NASH	Aerobic Resistance	+ 3 times	12	Standard care	Liver biopsy
Jia 2018 [20]	monocentre	461	Adults with NAFLD	Aerobic Resistance	+ ≥3 times	24	Standard care	Ultrasonography

Figures

Figure 1

Flowchart of the study selection process

	Cuthbertson 2016	Hallsworth 2015	Houghton 2017	Jia 2018	Pugh 2013	Pugh 2014	Shamsoddini 2015	Shojaee 2016	Sullivan 2012	Zelber-Sagi 2014	Zhang 2016
Random sequence generation (selection bias)	+	+	+	+	?	+	?	+	+	+	+
Allocation concealment (selection bias)	?	+	+	+	?	?	?	?	+	+	+
Blinding of participants and personnel (performance bias)	-	?	?	?	?	?	?	?	-	?	-
Blinding of outcome assessment (detection bias)	+	?	?	?	?	?	?	?	?	?	?
Incomplete outcome data (attrition bias)	+	+	+	+	+	+	+	+	+	+	+
Selective reporting (reporting bias)	+	+	+	+	+	+	+	+	+	+	+
Other bias	+	+	+	+	+	+	+	+	+	+	+

Figure 2

Methodological quality and risk of bias of the included trials

Figure 3

Subgroup analysis of the effects of physical activity intervention type on hepatic enzyme parameters (A: ALT, B: AST, C: GGT)

Figure 4

Subgroup analysis of the effects of physical activity intervention duration on hepatic enzyme parameters (A: ALT, B: AST, C: GGT)

Figure 5

Subgroup analysis of the effects of physical activity intervention type on serum lipid parameters (A: TC, B: TG, C: LDL-C, D: HDL-C)

Figure 6

Subgroup analysis of the effects of physical activity intervention duration on serum lipid parameters (A: TC, B: TG, C: LDL-C, D: HDL-C)

Subgroup analysis of the effects of physical activity intervention type on glucose metabolism parameters (A: fasting glucose, B: fasting insulin, C: HOMA-IR)

Figure 8

Subgroup analysis of the effects of physical activity intervention duration on glucose metabolism parameters (A: fasting glucose, B: fasting insulin, C: HOMA-IR)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [PRISMAchecklist.doc](#)