Ther Adv Gastroenterol
2017, Vol. 10(9) 701–713
DOI: 10.1177/1756283X17725977

Association between physical activity and risk of nonalcoholic fatty liver disease: a meta-analysis

Shanhu Qiu, Xue Cai, Zilin Sun, Ling Li, Martina Zügel, Jürgen Michael Steinacker and Uwe Schumann

Abstract

Background: Increased physical activity (PA) is a key element in the management of patients with nonalcoholic fatty liver disease (NAFLD); however, its association with NAFLD risk has not been systematically assessed. This meta-analysis of observational studies was to quantify this association with dose–response analysis.

Methods: Electronic databases were searched to January 2017 for studies of adults reporting the risk of NAFLD in relation to PA with cohort or case-control designs. Studies that reported sex-specific data were included as separate studies. The overall risk estimates were pooled using a random-effects model, and the dose–response analysis was conducted to shape the quantitative relationship.

Results: A total of 6 cohort studies from 5 articles with 32,657 incident NAFLD cases from 142,781 participants, and 4 case-control studies from 3 articles with 382 NAFLD cases and 302 controls were included. Compared with the lowest PA level, the highest PA level was associated with a risk reduction of NAFLD in cohort [RR (risk ratio) 0.79, 95% CI (confidence interval) 0.71–0.89] and case-control studies [OR (odds ratio) 0.43, 95% CI 0.27–0.68]. For cohort studies, both highest and moderate PA levels were superior to the light one in lowering NAFLD risk ($p_{\text{for interaction}} = 0.006$ and 0.02, respectively), and there was a log-linear dose–response association ($p_{\text{for nonlinearity}} = 0.10$) between PA and NAFLD risk [RR 0.82 (95% CI 0.73–0.91) for every 500 metabolic equivalent (MET)-minutes/week increment in PA].

Conclusions: Increased PA may lead to a reduced risk of NAFLD in a dose-dependent manner, and the current guideline-recommended minimum PA level that approximates to 500 MET-minutes/week is able to moderately reduce the NAFLD risk.

Keywords: dose–response, meta-analysis, nonalcoholic fatty liver disease, physical activity

Received: 4 April 2017; revised manuscript accepted: 7 June 2017.

Correspondence to:
Zilin Sun
Department of Endocrinology, Zhongda Hospital, Institute of Diabetes, School of Medicine, Southeast University, Dingjiaqiao No. 87, Nanjing 210009, China
sunzilin1963@126.com

Ling Li
Department of Endocrinology, Zhongda Hospital, Institute of Diabetes, School of Medicine, Southeast University, Dingjiaqiao No. 87, Nanjing 210009, China
li-ling 76@hotmail.com

Shanhu Qiu
Xue Cai
Zilin Sun
Department of Endocrinology, Zhongda Hospital, Institute of Diabetes, School of Medicine, Southeast University, Nanjing, China

Martina Zügel
Jürgen Michael Steinacker
Uwe Schumann
Division of Sports and Rehabilitation Medicine, Department of Internal Medicine, Ulm University, Ulm, Germany

Introduction

Nonalcoholic fatty liver disease (NAFLD) has become a widespread epidemic, with global prevalence estimates ranging approximately from 22% to 29% in the general population.[1] It encompasses a broad clinicopathologic spectrum from simple steatosis to nonalcoholic steatohepatitis, and can even progress to hepatocellular carcinoma.[2] Besides being the most common cause of liver disease, accumulating evidence indicates that NAFLD is associated with a substantial increase in risk for type 2 diabetes[3] and cardiovascular disease.[4] Consequently, approaches aimed at modifying risk factors for NAFLD are urgently in need to prevent or delay its onset as well as to limit its health-related burden.

Metabolic disorders characterized by insulin resistance including type 2 diabetes and central obesity have been well identified as significant contributing factors for NAFLD.[5] Large-scale cross-sectional studies have shown that these

disorders together with NAFLD are associated with lower levels of physical activity (PA) at any intensity on a daily basis compared with healthy controls.[6,7] Since increased PA plays a protective role against the development of type 2 diabetes and central obesity as well as against other risk factors related to NAFLD such as hypertension and dyslipidemia,[8–11] it is assumed that increased PA might be also effective in preventing NAFLD. Indeed, in recent years there is a notably growing interest in examining the association between PA and risk of NAFLD,[12–25] with most of them demonstrating a significant beneficial effect of PA in preventing NAFLD. However, no systematic reviews or meta-analyses have been conducted to quantify their association to date, which may provide a higher level of evidence than the individual study in general.

In addition, the recent guidelines recommend at least 150 min/week of moderate intensity or 75 min/week of vigorous intensity PA for all adults to reduce the risk of cardiovascular disease and type 2 diabetes as well as to improve cardiorespiratory fitness.[26,27] They further point out that additional health benefits can occur with extra PA, which might act in a dose–response manner.[27] However, it remains unknown whether the guideline-recommended minimum levels of PA, which are approximately equal to a minimal exercise amount of 500 metabolic equivalent (MET)-minutes/week,[26,27] are also sufficient to reduce the risk of NAFLD, and if there exists a dose–response relationship.

Therefore, the aims of the present study were to quantify the association between PA and risk of NAFLD in adults by meta-analyzing the observational studies and using dose–response analysis, as well as to explore the potential sources of heterogeneity that would affect the association by subgroup and meta-regression analyses.

Methods

This meta-analysis was reported in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines, and adhered to a predesigned protocol (PROSPERO CRD42016041233).

Search strategy

Studies of interest were identified by searching the electronic databases of *PubMed, Web of Science*, and the *Cochrane Library* from their inception through January, 2017 using words related to 'physical activity' (e.g. exercise, motor activity, sedentary lifestyle, metabolic equivalent*, physical activit*, inactivity, walking, training, running, cycling) and 'nonalcoholic fatty liver disease' (e.g. NAFLD, non-alcoholic fatty liver disease, nonalcoholic steatohepatitis, non-alcoholic steatohepatitis, steatosis, NAFLD, NASH). Reference lists from relevant major reviews and retrieved eligible articles were scrutinized to identify additional studies.

Inclusion and exclusion criteria

Studies written in English were included if they fulfilled the following criteria: (1) observational studies using a cohort or case-control design; (2) adult populations with ages $\geqslant$18 years; (3) outcome of interest was NAFLD that includes simple steatosis and nonalcoholic steatohepatitis but not the late stage liver diseases such as cirrhosis or hepatocellular carcinoma; and (4) effect estimates [i.e. relative risk (RR), odds ratio (OR)] of NAFLD associated with PA were provided or could be calculated. The diagnosis of NAFLD had to be defined with reference to the standard guidelines using noninvasive or invasive approaches.[2,5] Studies were excluded if they enrolled populations with secondary causes of hepatic steatosis such as alcohol, medication, and hepatitis viruses, or their effect estimates of interest could not be calculated.

Data extraction and quality assessment

A predesigned data collection form was used to extract the following information: first author, publication year, mean age, mean body mass index (BMI), proportion of men, geographical region, effect estimate with 95% confidence intervals (CIs) of the association between PA and NAFLD risk, number of cases and noncases (or controls), duration of follow-up, type and level of PA, method for ascertainment of NAFLD, and confounders adjusted.

The methodological quality of each included cohort study or case-control was assessed using the 9-stars-Newcastle-Ottawa scale.[28] All the data extraction and quality assessment were extracted and carefully checked by two independent authors (S.Q. and X.C.). If discrepancies occurred, they were solved by discussion referring back to the original studies.

Data synthesis and statistical analysis

For studies that provided only multiple levels of PA with distributions of cases and noncases, unadjusted effect estimates with 95% CIs were calculated directly.[29] For studies that reported effect estimates with or without adjustment for possible confounders, the maximally adjusted ones were selected for the primary analysis. For studies that assessed the association of NAFLD with different types of PA, data related to the leisure-time PA were initially chosen. For studies that reported sex-specific data, they were included as separate studies. In this meta-analysis, the RR, which was considered equivalent to the hazard ratio, was used for cohort studies, while the OR was employed for case-control studies. To assess the association of PA with NAFLD risk, both categorical and dose–response meta-analyses were conducted.

For categorical analysis, four levels of PA were generated as previously suggested: highest, moderate, light, and lowest.[30] Briefly, the highest and lowest PA levels corresponded to the highest and lowest groups in the included studies, respectively; and the moderate or light ones corresponded to the second and third-highest groups in studies that had more than two exposure categories, respectively. The overall estimates with 95% CIs for the associations of NAFLD with different PA levels *versus* the lowest one were calculated using a random-effects meta-analysis model, a model that is considered to be more conservative than the fixed-effects one.[31]

For dose–response analysis, the generalized least-squares trend estimation method described by Greenland and Longnecker was used.[32] The median of PA level expressed in MET-minutes/week for each category was assigned to the corresponding effect estimate. For studies that did not report the medians, they were imputed using the midpoints of the lower and upper bounds. For studies with an open-ended highest PA category, the width of PA in this category was assumed to be equal to that of its closest adjacent category.[30] For studies reporting the PA intensity without specification, the light, moderate, and vigorous intensity was respectively defined as 3, 5, and 9 METs.[30] Both the linear and nonlinear associations were assessed using a two-stage random-effects dose–response analysis. The nonlinear association was assessed by modeling the PA level with the use of restricted cubic splines with three knots at the 10th, 50th, and 90th percentiles of the exposure data. A p-value for nonlinearity was calculated using a null hypothesis that the coefficient of the second spline was equal to zero.

Heterogeneity was evaluated using the Cochran Q statistic and I^2 metric, with p-value for Cochran Q statistic <0.10 or I^2-value $>50\%$ representing statistical heterogeneity. The source of heterogeneity was assessed using subgroup analyses based on type of PA, validation of PA questionnaire, and adjustment for covariates. It was further assessed by meta-regression analyses of age (logarithmic transformed), sex (proportion of men), BMI, and duration of follow-up (if possible). Sensitivity analyses were performed by removing each study individually from the primary meta-analysis. Publication bias was evaluated by funnel plot asymmetry, and further assessed using Begg's rank correlation test and Egger's regression asymmetry test, with $p < 0.10$ indicative of significance. All the above statistical analyses were conducted using Stata Software (version 12.0 StataCorp, College Station, TX, USA).

Results

Characteristics of included studies

The details of the literature search and study selection are shown in Figure 1. Of the 1510 unique articles retrieved, 8 fulfilled the predefined inclusion criteria.[18–25] Among them, two had sex-specific data.[22,24] As a result, 10 studies were included in the meta-analysis, with 6 cohort[18–22] and 4 case-control studies.[23–25]

The characteristics of the included studies are described in Table 1. All studies were published between 2014 and 2016. For cohort studies, there were 32,657 incident NAFLD cases identified from 142,781 participants, who had a mean BMI of 22.6 kg/m^2 (ranged from 21.6 to 24.4 kg/m^2) at baseline, during a mean follow-up period of 6.30 years. For case-control studies, there were a total of 382 NAFLD cases and 302 controls. Most of these studies were conducted in Asian countries, and the others in European countries. All studies utilized questionnaires for assessment of PA, and the majority of them used ultrasonography for ascertainment of NAFLD except two using liver biopsy.[24] Overall, five studies provided effect estimates adjusted for confounding factors, although the consideration of these factors was different

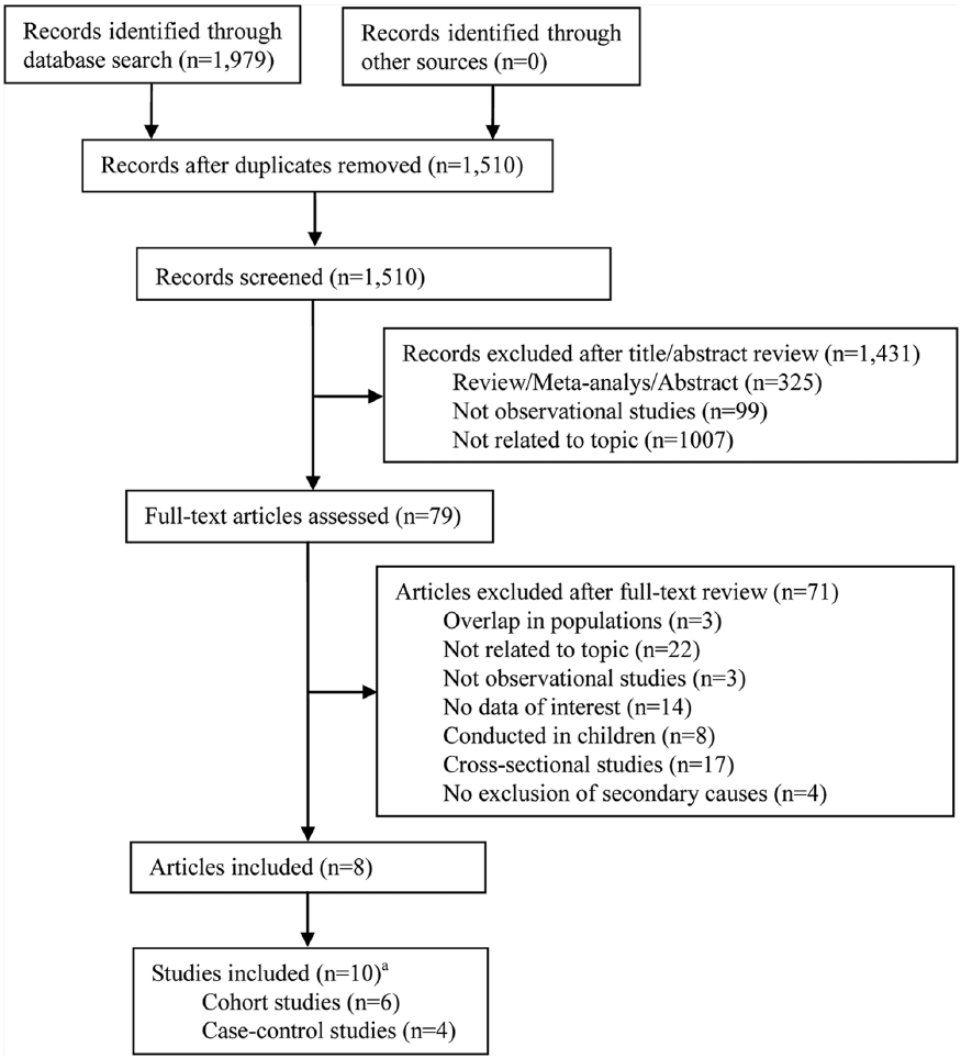

Figure 1. Flow diagram of literature search.
[a]The studies by Hashimoto and colleagues[22] and Noto and colleagues[24] had sex-based data.

from each study. The methodological quality of included cohort studies was high, with a mean score of 7.7.

PA and NAFLD risk in cohort studies

Categorical analysis: The associations between different PA levels and NAFLD risk among adults are shown in Figure 2. Compared with the lowest PA level, which was defined as physically inactive or sedentary in the included studies, the highest PA level was associated with a decreased risk of NAFLD (six studies; RR 0.79, 95% CI 0.71–0.89; I^2 = 59.1%). The moderate and light PA levels were also associated with reduced risks of NAFLD compared with the lowest one (four studies; RR 0.87, 95% CI 0.83–0.91, I^2 <1%, and four studies; RR 0.93, 95% CI 0.90–0.96, I^2 <1%; respectively). Further analysis using the test for interaction suggested that the highest and moderate PA levels were superior to the light one in lowering NAFLD risk ($p_{\text{for interaction}}$ = 0.006 and 0.02, respectively).

Subgroup, meta-regression, and sensitivity analyses as well as publication bias that evaluated the association between the highest PA level (*versus* the lowest one) and NAFLD risk were conducted as follows. Subgroup analyses showed that the association was more conservative in studies using validated PA questionnaires (RR 0.78, 95% CI 0.68–0.89) than those who did not (RR 0.89,

Table 1. Characteristics of included studies in this meta-analysis.

Study	Age (y), sex[a], %	Total sample size	Categories of PA levels[b]	Adjusted covariates
Cohort studies				
Tsunoda *et al.*,[18] Japan	47.8, 39.5	7803	Cat 1: PA ⩾ 3 times/week Cat 2: PA 2 times/week Cat 3: PA 1 times/week Cat 4: PA < 1 times/week	Age, sex, BMI, alcohol consumption (never or low-moderate), smoking, family history of liver disease, alanine transaminase, γ-glutamyltransferase, hypertension, diabetes, dyslipidemia, vegetable intake, other intensity types of PA and propensity
Sung *et al.*,[19] Korea	40.5, 47	126,811	Cat 1: PA sessions/week ⩾ 5 Cat 2: PA sessions/week 3–4 Cat 3: PA sessions/week 1–2 Cat 4: PA sessions/week 0	Age, sex, center, year of screening exam, smoking status, alcohol intake, education level, BMI, diabetes, hypertension, cardiovascular disease, and change in BMI between baseline and follow up
Kwak *et al.*,[20] Korea	51.4, 51.6	1373	Cat 1: ⩾1504 MET-min/week (men) ⩾1368 MET-min/week (women) Cat 2: 1004–1500 MET-min/week (men) 912–1365 MET-min/week (women) Cat 3: 522–996 MET-min/week (men) 486–900 MET-min/week (women) Cat 4: 10–547 MET-min/week (men) 68–480 MET-min/week (women) Cat 5: Inactive	Age, sex, BMI, smoking, hypertension, diabetes, soft drink consumption, coffee consumption, change in waist circumference during follow up, visceral adipose tissue area, subcutaneous adipose tissue area, and HOMA-IR
Li *et al.*,[21] China	36.7, 100	2367	Cat 1: PA everyday Cat 2: PA often Cat 3: PA occasionally Cat 4: PA never or seldom	None
Hashimoto *et al.*,[22] Japan				
Women	41.4, 0	1847	Cat 1: Regular PA Cat 2: No regular PA	None
Men	42.4, 100	2580		
Case-control studies				
Miele *et al.*,[23] Italy	51.5, 64.5	280	Cat 1: >1 activity/week Cat 2: ⩽1 activity/week	Age, drinking habits, additional use of salt, meat intake, and PA
Noto *et al.*,[24] Japan				
Women	57.7, 0	119	Cat 1: Regular PA Cat 2: No regular PA	None
Men	46.7, 100	130		
Katsagoni *et al.*,[25] Greece	45.2, 68.4	155	PA as a continuous variable	Age, sex, waist circumference, HOMA-IR, adiponectin, and TNF-α

BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; MET, metabolic equivalent; PA, physical activity; TNF-α, tumor necrosis factor-α.
[a]Data represented proportions of men.
[b]Four categories of PA levels were generated, which were highest, moderate, light, and lowest. For each included study, the highest and lowest PA categories corresponded to the highest and lowest groups, respectively. For studies with ⩾3 PA categories, the second and third-highest PA categories corresponded to the moderate and light groups, respectively.

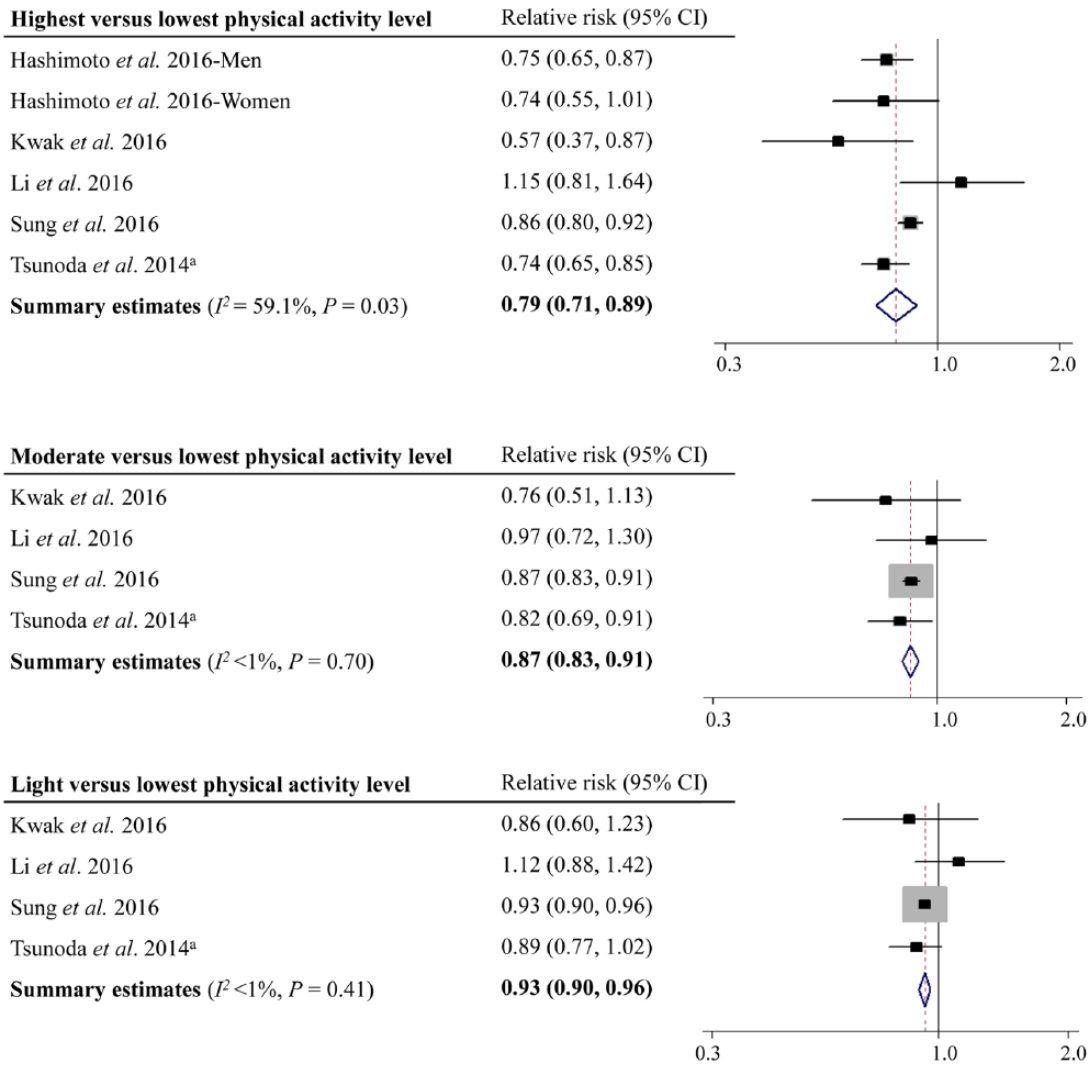

Figure 2. Pooled estimates of the relative risks of NAFLD associated with PA.
CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; PA, physical activity.
[a]Data were averaged from all the three groups with different PA intensities.

95% CI 0.58–1.37), and seemed to be unlikely to be affected by the types of PA (leisure-time *versus* total PA, $p_{\text{for interaction}} = 0.28$; Table 2). This association remained significant after adjusting for a single traditional risk factor for NAFLD including smoking, obesity, glucose control, blood pressure, or lipid profiles, as well as for a cluster of them (all $p < 0.05$; Table 2). Interestingly, the strength of this association tends to be weaker in studies that take into account changes of BMI during the follow-up period compared with those who did not ($p_{\text{for interaction}} = 0.16$; Table 2).

Meta-regression analyses suggested that the association was statically moderated by age (β coefficient 0.30, $p = 0.04$), but was not affected by sex (β coefficient 1.00, $p = 0.54$), BMI (β coefficient 1.10, $p = 0.30$), or follow-up periods (β coefficient 0.98, $p = 0.59$). Sensitivity analysis by removing each individual study showed that the primary RRs were unlikely to be substantially altered. The shape of the funnel plot seems to be asymmetrical (Figure 3), but no statistical publication bias was detected using the Begg's ($p = 0.71$) or Egger's test ($p = 0.49$).

Dose–response analysis: Only two cohort studies[19,20] allowed the quantitative estimation of PA in MET-minutes/week. The departure from a log-linear association between PA and risk of NAFLD among adults was not significant (p for nonlinearity = 0.10, and for linearity <0.001;

Table 2. Subgroup analyses of relative risk of NAFLD for highest *versus* lowest PA level in cohort studies.

Variable	Number of studies	Effect estimates		Heterogeneity	
		RR	95% CI	I^2 (%)	*p*
Sex					
Male	2	0.90	0.59–1.36	79.2	0.03
Female	1	0.74	0.55–1.01	NA	NA
Mixed	3	0.77	0.66–0.91	70.4	0.03
PA type[a]					
TPA	1	0.66	0.46–0.94	NA	NA
LTPA	5	0.81	0.72–0.90	57.5	0.05
PA assessment					
Validated	4	0.78	0.68–0.89	52.8	0.10
Not validated	2	0.89	0.58–1.37	80.9	0.02
Adjustment					
Yes	3	0.77	0.66–0.91	70.4	0.03
No	3	0.83	0.66–1.05	60.1	0.08
Adjusted for …					
(1) Smoking					
Yes	3	0.77	0.66–0.91	70.4	0.03
No	3	0.83	0.66–1.05	60.1	0.08
(2) Body mass index/obesity					
Yes	3	0.77	0.66–0.91	70.4	0.03
No	3	0.83	0.66–1.05	60.1	0.08
(3) Glucose control/diabetes					
Yes	3	0.77	0.66–0.91	70.4	0.03
No	3	0.83	0.66–1.05	60.1	0.08
(4) Blood pressure/hypertension					
Yes	2	0.71	0.58–0.86	23.3	0.25
No	4	0.83	0.73–0.95	53.6	0.09
(5) Lipid profiles/dyslipidemia					
Yes	2	0.71	0.58–0.86	23.3	0.25
No	4	0.83	0.73–0.95	53.6	0.09
(6) A cluster of at least 3 traditional risk factors[b]					
Yes	3	0.77	0.66–0.91	70.4	0.03
No	3	0.83	0.66–1.05	60.1	0.08
(7) Changes in body mass index during follow-up period					
Yes	1	0.86	0.80–0.92	NA	NA
No	5	0.77	0.67–0.88	44.7	0.12

CI, confidence interval; LTPA, leisure-time physical activity; NA, not applicable; NAFLD, nonalcoholic fatty liver disease; PA, physical activity; RR, relative risk; TPA, total physical activity.

[a]The study from Kwak and colleagues reported data on TPA and LTPA, but in this subgroup analysis data from TPA were chosen.[20]

[b]The traditional risk factors included metabolic factors related to obesity, diabetes, hypertension, or dyslipidemia.

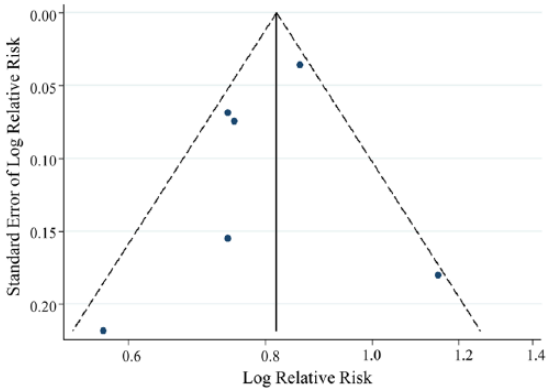

Figure 3. Funnel plot with pseudo 95% CIs for publication bias in studies of the association between PA and risk of NAFLD.
CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; PA, physical activity.

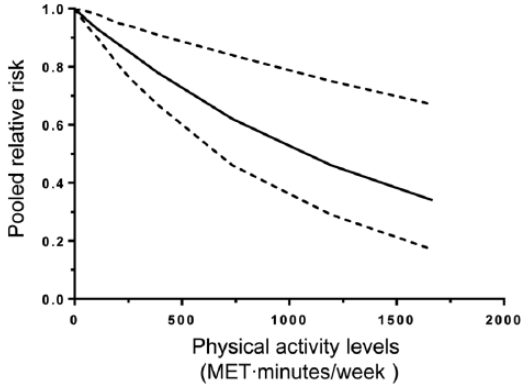

Figure 4. Dose–response association between PA assessed by metabolic equivalent-min/week and risk of NAFLD.
MET, metabolic equivalent; NAFLD, nonalcoholic fatty liver disease; PA, physical activity.
The solid and dotted splines of the graph indicate the pooled relative risk and 95% confidence intervals, respectively.

Figure 4). Pooled results showed that a 500 MET-minutes/week incrementally higher PA was associated with an 18% risk reduction of NAFLD (RR 0.82, 95% CI 0.73–0.91), and the magnitude of this reduction continued to be enlarged with more PA when compared with 500 MET-minutes/week PA [e.g. 1000 MET-minutes/week led to an 33% risk reduction (RR 0.67, 95% CI 0.54–0.83, $p_{\text{for interaction}} = 0.10$)].

PA and NAFLD risk in case-control studies

Categorical analysis: A total of three studies provided data comparing the risk of NAFLD with the assigned highest *versus* lowest PA level, and the pooled result showed that the highest PA level significantly reduced the risk of NAFLD (OR 0.43, 95% CI 0.27–0.68; $I^2 < 1\%$). Subgroup analysis suggested that this association was similar across different types of PA (recreational *versus* leisure-time PA, $p_{\text{for interaction}} = 0.81$) or methods for NAFLD diagnosis (ultrasonography *versus* liver biopsy, $p_{\text{for interaction}} = 0.81$). Sensitivity analysis by excluding one study at a time showed that the primary association was not statistically influenced by any particular study. There was no significant evidence of publication bias as indicated by the Begg's ($p = 0.30$) or Egger's test ($p = 0.27$).

Dose–response analysis: Since none of the case-control studies provided individual effect sizes corresponding to at least three different levels of PA, assessment of the linear or nonlinear association of NAFLD risk with PA seemed to be impossible. Yet the study by Katsagoni and colleagues, who reported data using PA level as the continuous variable,[25] suggested that the odds of having NAFLD was reduced by 26% for every 100 MET-minutes/day incrementally higher PA (OR 0.74, 95% CI 0.61–0.89); which is alternatively, a reduction by 19% per 500 MET-minutes/week incrementally higher PA (OR 0.81, 95% CI 0.70–0.92).

Discussion

Summary of main findings

The present meta-analysis shows that increased PA was associated with a reduced risk of NAFLD among adults, which was consistently observed in cohort and case-control studies. This association seemed to act in a log-linear dose–response manner among adults, and remained statistically significant with adjustment for traditional risk factors for NAFLD, indicating that PA might be an independent protective factor against NAFLD. It further shows that this association was not affected by the types of PA, but was positively moderated by age. Of note, this meta-analysis suggests that the guideline-recommended minimal levels of PA were sufficient for a moderate reduction in NAFLD risk. However, a higher amount of PA may be required in order to obtain a considerable larger risk reduction.

Interpretations

Recent guideline suggests that unhealthy lifestyles including physical inactivity play a key role in the development of NAFLD, and that the assessment

of PA habits is worth being conducted in a comprehensive NAFLD screening programme.[2] However, such recommendations are largely based on the results from a single population-based cross-sectional study by Gerber and colleagues[7] rather than a meta-analysis or a systematic review, although that study was well-conducted and the conclusion was well-balanced. Therefore, our finding of this meta-analysis that PA might lead to a decreased risk of NAFLD based on results from observational studies and in particular of cohort studies seems to provide higher level of evidence in support of the aforementioned notions.

Recent evidence well-documents that PA is effective in modifying liver fat and serum alanine aminotransferase among patients who already had NAFLD;[33–35] however, there is so far, no standardized or straightforward recommendation for the amount of PA aiming to prevent NAFLD in current guidelines. The national PA recommendation of engaging in at least 150 min/week of moderate PA or 75 min/week of vigorous activity for adults [26,27] has shown to be associated with a substantially reduced risk of cardiovascular disease,[36] heart failure,[30] and type 2 diabetes.[27] Given this evidence and in light of the lowered NAFLD risk related to 500 MET-minutes/week incrementally higher PA as shown in our dose–response analysis, it seems reasonable to prescribe this guideline-recommended minimum PA level for NAFLD prevention in clinical practice. Notably, as evidenced by the categorical and subgroup analyses as well as the log-linear dose–response association, one should be aware that any amount of PA in any type (e.g. leisure-time or recreational PA) is better than physical inactivity, and that the higher the amount of PA, the more the risk reduction of NAFLD. Therefore, interventions with the aim to increase PA, such as using pedometers,[37] might be worth recommending. Yet as suggested by Finelli and Tarantino, one should also keep in mind that PA requires to be maintained for long periods (e.g. months or years) at an increased level in order to counteract the development or progression of NAFLD.[38]

Several lines of evidence recently suggest that there might be a sex difference in the association between PA and risk of fatty liver including NAFLD.[24,39] But, their findings were inconsistent. Our results as indicated by the subgroup and meta-regression analyses therefore provided a piece of evidence in addressing this concern, showing that men did not substantially differ from women regarding the NAFLD risk reduction from PA. Interestingly, our results showed that the magnitude of risk reduction of NAFLD was larger in participants with older age. This is definitely encouraging since older participants experience a higher chance of developing NAFLD[40] and are more likely to show impaired physical capacity compared with younger ones. Moreover, although independent of changes in BMI during the follow-up period, the strength of the association between PA and NAFLD risk became weaker when considering it as a possible confounder. This may partly imply the important role of weight change in altering NALFD risk.

Despite a statistically nonsignificant difference between studies using validated questionnaires and those not regarding the association of PA with risk of NALFD, our subgroup analysis showed that the former exhibited a more conservative and stronger association than the latter. This might indicate that studies failing to use validated PA questionnaires would probably underestimate the observed association of PA with risk of NAFLD. In contrast to the methods for PA assessment, our results from the case-control studies did not provide adequate evidence that the risk of NAFLD associated with PA would be significantly affected by approaches for NAFLD ascertainment (that is, liver biopsy *versus* ultrasonography), although it is well established that liver biopsy outperforms ultrasonography in diagnosing NALFD[41] and is considered to be the gold standard for characterizing liver histology and to stage fibrosis.[2]

There are several potential mechanisms that may underlie the observed inverse association between PA and risk of NAFLD. Firstly, some studies have noted that PA might improve appetite control by enhancing satiety signaling;[42] whereas a good appetite is closely associated with a high-calorie or excess fat intake and obesity, which have been recognized to be central to the development of NAFLD.[2] Secondly, PA not only reduces free fatty acids in circulation but also increases the uptake and utilization of fatty acids in liver and skeletal muscle,[33,43] leading to subsequently reduced hepatic fat accumulation. Thirdly, hepatic and muscle insulin resistance is considered the pathophysiological hallmark of NAFLD,[44] which could be ameliorated directly by increased PA probably through a reduction in hepatic fat

content[45] or indirectly through an increase in muscle glucose transporter 4 expression and muscle glycogen synthase activity.[46]

Strengths and limitations

The primary strength of our study is that the large sample size from case-control and prospective cohort studies increases the statistical power to detect the association between PA and NAFLD risk. In addition, the dose–response analysis allowed us to investigate the shape of the possible association. Moreover, the main findings observed in our study were robust as indicated by the sensitivity analyses, and the existing heterogeneities could be explained by age or partly by other variables like the validation of PA questionnaires and the adjusted covariates including blood pressure, lipid profiles, and changes in BMI.

However, several possible limitations of our study should be mentioned. Firstly, despite of the maximally adjusted effect estimates chosen for the primary analysis, results from the meta-analysis cannot prove causality since they are subject to residual confounding. Our meta-analysis showed that the association of NAFLD risk with PA was unlikely to be affected by any single one or a cluster of the traditional risk factors for NAFLD including smoking, obesity, glucose control, blood pressure, and lipid profiles. However, we cannot further explore the potential influences from other confounding factors related to unhealthy lifestyle behaviors (e.g. prolonged sedentary time[15]) and healthy ones (e.g. high coffee consumption[47,48]) because of the fact that the majority of included studies failed to provide such data.

Secondly, both unadjusted and the maximally adjusted estimates were pooled together in our meta-analysis, which may contribute to the existing heterogeneity, despite that there was a nonsignificant difference between them. Thirdly, although validated questionnaires had been used in most cohort studies to assess PA levels, they might still not reflect the true ones. This lies in the fact that subjectively measured PA (e.g. by questionnaires) is more likely to be subject to recall and response bias compared with the objectively measured one (e.g. by pedometers), resulting in underestimated or overestimated PA levels.[49] This might lead to a risk of misclassification bias. Fourthly, there is evidence that both aerobic and resistance exercise exert beneficial effects against the risk of NAFLD. However, the small number of included studies limited our further analysis on this topic. Fifthly, as all the cohort studies were exclusively from Asian origins, our main findings might be not representative for other populations like Whites or Hispanics who might have a different ethnical and genetic background. Furthermore, our study did not provide results regarding the association of PA with risks of NAFLD subtypes like nonalcoholic steatohepatitis, but there is epidemiological evidence from the cross-sectional study that increased PA might be correlated with a reduced OR of having nonalcoholic steatohepatitis.[50] Finally, the inclusion of only English-language and published studies might introduce some selection and publication bias. Moreover, the statistical power of the publication bias assessment and meta-regression analyses might be weakened because of the limited number of studies included.

In conclusion, our meta-analysis indicated that increased PA might be dose-dependently associated with a lower risk of NAFLD in adults. The current guideline-recommended minimum PA level (500 MET-minutes/week) was able to moderately reduce NAFLD risk; however, doses of PA in excess of that suggested amount might be required to obtain a more robust risk reduction. Future studies with large-scale prospective cohort designs are required to explore the association of risk for NAFLD and in particular its subtype nonalcoholic steatohepatitis with objectively measured PA levels or at least self-reported ones assessed by validated questionnaires, where PA levels are categorized into aerobic or resistance types, among sex-based or age-stratified populations.

Acknowledgements

Shanhu Qiu conducted the study, collected and analysed the data, and wrote the manuscript. Xue Cai collected the data. Martina Zügel and Jürgen Michael Steinacker contributed to the introduction, reviewed/edited the manuscript. Zilin Sun, Ling Li, and Uwe Schumann designed the study, contributed to the discussion, and edited the manuscript. All authors read and approved the final manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

1. Younossi ZM, Koenig AB, Abdelatif D, *et al.* Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; 64: 73–84.
2. European Association for the Study of the Liver, European Association for the Study of Diabetes and European Association for the Study of Obesity. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016; 64: 1388–1402.
3. Ballestri S, Zona S, Targher G, *et al.* Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2016; 31: 936–944.
4. Lonardo A, Sookoian S, Pirola CJ, *et al.* Non-alcoholic fatty liver disease and risk of cardiovascular disease. *Metabolism* 2016; 65: 1136–1150.
5. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *JAMA* 2015; 313: 2263–2273.
6. Zhao G, Ford ES, Li C, *et al.* Physical activity in U.S. older adults with diabetes mellitus: prevalence and correlates of meeting physical activity recommendations. *J Am Geriatr Soc* 2011; 59: 132–137.
7. Gerber L, Otgonsuren M, Mishra A, *et al.* Non-alcoholic fatty liver disease (NAFLD) is associated with low level of physical activity: a population-based study. *Aliment Pharmacol Ther* 2012; 36: 772–781.
8. Aune D, Norat T, Leitzmann M, *et al.* Physical activity and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis. *Eur J Epidemiol* 2015; 30: 529–542.
9. Stephens SK, Cobiac LJ and Veerman JL. Improving diet and physical activity to reduce population prevalence of overweight and obesity: an overview of current evidence. *Prev Med* 2014; 62: 167–178.
10. Huai P, Xun H, Reilly KH, *et al.* Physical activity and risk of hypertension: a meta-analysis of prospective cohort studies. *Hypertension* 2013; 62: 1021–1026.
11. Riccardi G, Vaccaro O, Costabile G, *et al.* How well can we control dyslipidemias through lifestyle modifications? *Curr Cardiol Rep* 2016; 18: 66.
12. Bae JC, Suh S, Park SE, *et al.* Regular exercise is associated with a reduction in the risk of NAFLD and decreased liver enzymes in individuals with NAFLD independent of obesity in Korean adults. *PLoS One* 2012; 7: e46819.
13. Koehler EM, Schouten JN, Hansen BE, *et al.* Prevalence and risk factors of non-alcoholic fatty liver disease in the elderly: results from the Rotterdam study. *J Hepatol* 2012; 57: 1305–1311.
14. Kwak MS, Kim D, Chung GE, *et al.* Role of physical activity in nonalcoholic fatty liver disease in terms of visceral obesity and insulin resistance. *Liver Int* 2015; 35: 944–952.
15. Ryu S, Chang Y, Jung HS, *et al.* Relationship of sitting time and physical activity with non-alcoholic fatty liver disease. *J Hepatol* 2015; 63: 1229–1237.
16. Trovato FM, Martines GF, Brischetto D, *et al.* Fatty liver disease and lifestyle in youngsters: diet, food intake frequency, exercise, sleep shortage and fashion. *Liver Int* 2016; 36: 427–433.
17. Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, *et al.* Role of leisure-time physical activity in nonalcoholic fatty liver disease: a population-based study. *Hepatology* 2008; 48: 1791–1798.
18. Tsunoda K, Kai Y, Uchida K, *et al.* Physical activity and risk of fatty liver in people with different levels of alcohol consumption: a prospective cohort study. *BMJ Open* 2014; 4: e005824.
19. Sung KC, Ryu S, Lee JY, *et al.* Effect of exercise on the development of new fatty liver and the resolution of existing fatty liver. *J Hepatol* 2016; 65: 791–797.
20. Kwak MS, Kim D, Chung GE, *et al.* The preventive effect of sustained physical activity on incident nonalcoholic fatty liver disease. *Liver Int* 2017; 37: 919–926.
21. Li C, Xing JJ, Shan AQ, *et al.* Increased risk of nonalcoholic fatty liver disease with occupational stress in Chinese policemen: a 4-year cohort study. *Medicine (Baltimore)* 2016; 95: e5359.
22. Hashimoto Y, Hamaguchi M, Fukuda T, *et al.* BMI history and risk of incident fatty liver: a population-based large-scale cohort study. *Eur J Gastroenterol Hepatol* 2016; 28: 1188–1193.

23. Miele L, Dall'armi V, Cefalo C, *et al*. A case-control study on the effect of metabolic gene polymorphisms, nutrition, and their interaction on the risk of non-alcoholic fatty liver disease. *Genes Nutr* 2014; 9: 383.

24. Noto H, Tokushige K, Hashimoto E, *et al*. Questionnaire survey on lifestyle of patients with nonalcoholic steatohepatitis. *J Clin Biochem Nutr* 2014; 55: 191–195.

25. Katsagoni CN, Georgoulis M, Papatheodoridis GV, *et al*. Associations between lifestyle characteristics and the presence of nonalcoholic fatty liver disease: a case-control study. *Metab Syndr Relat Disord* 2016; 15: 72–79.

26. US Department of Health and Human Services (HHS). Physical activity guidelines for Americans, http://www.health.gov/paguidelines/guidelines/chapter1.aspx (2008, accessed 10 August 2016).

27. Colberg SR, Sigal RJ, Fernhall B, *et al*. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care* 2010; 33: e147–e167.

28. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; 25: 603–605.

29. Liu M, Wu L and Yao S. Dose-response association of screen time-based sedentary behaviour in children and adolescents and depression: a meta-analysis of observational studies. *Br J Sports Med* 2015; 50: 1252–1258.

30. Pandey A, Garg S, Khunger M, *et al*. Dose-response relationship between physical activity and risk of heart failure: a meta-analysis. *Circulation* 2015; 132: 1786–1794.

31. Higgins JPT, Green S and Cochrane Collaboration. *Cochrane handbook for systematic reviews of interventions*. Chichester, England; Hoboken, NJ: Wiley-Blackwell, 2008, pp. xxi, 649.

32. Greenland S and Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992; 135: 1301–1309.

33. Smart NA, King N, McFarlane JR, *et al*. Effect of exercise training on liver function in adults who are overweight or exhibit fatty liver disease: a systematic review and meta-analysis. *Br J Sports Med*. Epub ahead of print 17 June 2016. DOI: 10.1136/bjsports-2016-096197.

34. Orci LA, Gariani K, Oldani G, *et al*. Exercise-based interventions for nonalcoholic fatty liver disease: a meta-analysis and meta-regression. *Clin Gastroenterol Hepatol* 2016; 14: 1398–1411.

35. Zelber-Sagi S, Godos J and Salomone F. Lifestyle changes for the treatment of nonalcoholic fatty liver disease: a review of observational studies and intervention trials. *Therap Adv Gastroenterol* 2016; 9: 392–407.

36. Sattelmair J, Pertman J, Ding EL, *et al*. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation* 2011; 124: 789–795.

37. Qiu S, Cai X, Chen X, *et al*. Step counter use in type 2 diabetes: a meta-analysis of randomized controlled trials. *BMC Med* 2014; 12: 36.

38. Finelli C and Tarantino G. Have guidelines addressing physical activity been established in nonalcoholic fatty liver disease? *World J Gastroenterol* 2012; 18: 6790–6800.

39. Miyake T, Kumagi T, Hirooka M, *et al*. Significance of exercise in nonalcoholic fatty liver disease in men: a community-based large cross-sectional study. *J Gastroenterol* 2015; 50: 230–237.

40. Wong VW, Wong GL, Yeung DK, *et al*. Incidence of non-alcoholic fatty liver disease in Hong Kong: a population study with paired proton-magnetic resonance spectroscopy. *J Hepatol* 2015; 62: 182–189.

41. Bohte AE, van Werven JR, Bipat S, *et al*. The diagnostic accuracy of US, CT, MRI and 1H-MRS for the evaluation of hepatic steatosis compared with liver biopsy: a meta-analysis. *Eur Radiol* 2011; 21: 87–97.

42. Beaulieu K, Hopkins M, Blundell J, *et al*. Does habitual physical activity increase the sensitivity of the appetite control system? A systematic review. *Sports Med* 2016; 46: 1897–1919.

43. Johnson NA and George J. Fitness versus fatness: moving beyond weight loss in nonalcoholic fatty liver disease. *Hepatology* 2010; 52: 370–381.

44. Bugianesi E, McCullough AJ and Marchesini G. Insulin resistance: a metabolic pathway to chronic liver disease. *Hepatology* 2005; 42: 987–1000.

45. Haufe S, Engeli S, Budziarek P, *et al*. Cardiorespiratory fitness and insulin sensitivity in overweight or obese subjects may be linked through intrahepatic lipid content. *Diabetes* 2010; 59: 1640–1647.

46. O'Gorman DJ, Karlsson HK, McQuaid S, *et al*. Exercise training increases insulin-stimulated glucose disposal and GLUT4 (SLC2A4)

protein content in patients with type 2 diabetes. *Diabetologia* 2006; 49: 2983–2992.

47. Zelber-Sagi S, Salomone F, Webb M, *et al.* Coffee consumption and nonalcoholic fatty liver onset: a prospective study in the general population. *Transl Res* 2015; 165: 428–436.
48. Shen H, Rodriguez AC, Shiani A, *et al.* Association between caffeine consumption and nonalcoholic fatty liver disease: a systemic review and meta-analysis. *Therap Adv Gastroenterol* 2016; 9: 113–120.
49. Prince SA, Adamo KB, Hamel ME, *et al.* A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. *Int J Behav Nutr Phys Act* 2008; 5: 56.
50. Da Silva HE, Arendt BM, Noureldin SA, *et al.* A cross-sectional study assessing dietary intake and physical activity in Canadian patients with nonalcoholic fatty liver disease vs healthy controls. *J Acad Nutr Diet* 2014; 114: 1181–1194.